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Technical Report Series
No. 323

COMPLETED

TOXICOLOGY AND CARCINOGENESIS STUDIES OF DIMETHYL METHYLPHOSPHONATE

(CAS NO. 756-79-6)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of disease. By bringing together the relevant programs, staff, and resources from the U.S. Public Health Service, DHHS, the National Toxicology Program has centralized and strengthened activities relating to toxicology research, testing and test development/validation efforts, and the dissemination of toxicological information to the public and scientific communities and to the research and regulatory agencies.

The NTP is made up of four charter DHHS agencies: the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS.

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF DIMETHYL METHYLPHOSPHONATE

(CAS NO. 756-79-6)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
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NOTE TO THE READER

This study was performed under the direction of the National Institute of Environmental Health Sciences as a function of the National Toxicology Program. The studies described in this Technical Report have been conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. Animal care and use were in accordance with the U.S. Public Health Service Policy on Humane Care and Use of Animals. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for public peer review.

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to identify any mistakes so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP. Comments and questions about the National Toxicology Program Technical Reports on Toxicology and Carcinogenesis Studies should be directed to Dr. J.E. Huff, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709 (919-541-3780).

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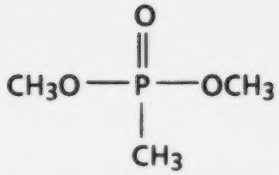

DIMETHYL METHYLPHOSPHONATE

CAS No. 756-79-6

$C_3H_9O_3P$ Molecular weight 124.1

Synonyms: Fyrol DMMP; Methyl phosphonic acid, dimethyl ester; DMMP; Methanephosphonic acid dimethyl ester; Dimethyl methanephosphonate

ABSTRACT

Dimethyl methylphosphonate (98% pure) is one of four chemicals nominated by the U.S. Army for toxicology and carcinogenesis studies because it was being considered for use to simulate the physical and spectroscopic (but not the biologic) properties of anticholinesterase (nerve) agents. Dimethyl methylphosphonate is also used as a flame retardant, a preignition additive for gasoline, an antifoam agent, a plasticizer and stabilizer, a textile conditioner and antistatic agent, and an additive for solvents and low-temperature hydraulic fluids. The United States produces 0.2-2 million pounds (91,000-910,000 kg) of dimethyl methylphosphonate per year. Gavage was chosen as the route of administration for all four candidate "simulants" to mimic potential oral exposure.

Experimental Design: Dimethyl methylphosphonate was administered in corn oil by gavage to male and female F344/N rats and B6C3F$_1$ mice in single-administration, 15-day, and 13-week studies to obtain toxicity data, to establish dose levels for the 2-year studies, and to identify target tissues. Additional studies were also performed to determine toxicity to the reproductive system of male F344/N rats and B6C3F$_1$ mice and to study the potential for genetic damage in bacteria, mammalian cells, and Drosophila.

Single-Administration Studies: In the single-administration studies, dimethyl methylphosphonate was given to rats and mice at doses up to 6,810 mg/kg body weight. No compound-related deaths were seen in male or female rats or male mice; two high dose female mice died. Rats exhibited inactivity, unsteady gait, and prostration after dosing; mice were inactive after dosing.

Fifteen-Day Studies: Rats and mice received doses of 0, 1,250, 2,500, 5,000, 10,000, or 15,000 mg/kg dimethyl methylphosphonate per day. Compound-related deaths occurred in the three highest dose groups of rats and the two highest dose groups of mice. Rats receiving doses of 2,500 mg/kg or higher were inactive and at 5,000 or 10,000 mg/kg had an unsteady gait after dosing; mice exhibited inactivity, shallow breathing, and prostration at doses of 10,000 mg/kg and higher. No lesions were reported in rats. Nonneoplastic lesions of the stomach were seen in some male mice at doses of 1,250 mg/kg and higher and in some female mice at doses of 5,000 mg/kg and higher.

Thirteen-Week Studies: Dimethyl methylphosphonate was given at doses up to 8,000 mg/kg per day. Compound-related deaths occurred at 2,000, 4,000, and 8,000 mg/kg in rats and at 4,000 and 8,000 mg/kg in mice. Mean body weights of rats at 1,000 mg/kg and mice at 2,000 mg/kg were similar to those of the vehicle controls; decreased weight gain was seen at higher doses. No compound-related clinical signs were reported. Minimal to mild renal and testicular lesions were seen at all doses in male rats, but the severity of these lesions did not increase with increasing dose of the chemical. No apparent target tissues were identified in female rats or male and female mice.

Doses selected for the 2-year studies were based on body weight effects and mortality seen in the 13-week studies; the lesions seen in the kidney of male rats at the end of the 13-week studies were judged not to be life threatening. In the 2-year studies, dimethyl methylphosphonate was administered in corn oil by gavage at doses of 0, 500, or 1,000 mg/kg per day to groups of 50 F344/N rats of each sex and at 0, 1,000, or 2,000 mg/kg per day to groups of 50 $B6C3F_1$ mice of each sex. All animals were dosed 5 days per week for 103 weeks.

Body Weight and Survival in the Two-Year Studies: Mean body weights of high dose male rats were 5%-10% lower than those of the vehicle controls between weeks 28 and 76 and were 10%-24% lower between weeks 80 and 104. Mean body weights of high dose female rats were 8%-12% lower than those of the vehicle controls after week 80. Survival of male rats was greater than 50% in all groups until week 80, and after this time, survival decreased in both dose groups, with the survival at the end of the study being 27/50 in vehicle control, 17/50 in low dose, and 4/50 in high dose groups. Survival of low dose female rats was comparable to that of the vehicle controls, but final survival of high dose female rats was decreased (vehicle control, 30/50; low dose, 33/50; high dose, 23/50). No other compound-related clinical signs were observed.

Mean body weights of high dose male mice were 7%-16% lower than those of the vehicle control males between weeks 36 and 76, and those of high dose female mice were 6%-12% lower between weeks 88 and 103. Decreased survival between weeks 23 and 45 in high dose male mice was associated with fighting. Seventeen high dose male and 22 high dose female mice died during week 45; these deaths were associated with the accidental administration of a dose mixture that had a concentration 34% greater than the targeted amount. Eleven low dose male mice died on the same day during week 77. By the end of the study, 29/50 vehicle control, 12/50 low dose, and 0/50 high dose male mice were alive; 41/50, 30/50, and 2/50 female mice survived to the end of the study.

Renal Effects in the Two-Year Studies: Administration of dimethyl methylphosphonate to male rats increased the average severity of nephropathy and caused mineralization (calcification) of the collecting tubules in the renal papilla (12/50; 41/50; 36/49), hyperplasia of the transitional epithelium lining the renal pelvis and overlying the renal papilla (0/50; 23/50; 21/49), and focal hyperplasia of the renal tubular epithelium (0/50; 8/50; 9/49). Administration of dimethyl methylphosphonate to male rats was also associated with the occurrence of rare renal tubular cell adenocarcinomas (0/50; 2/50; 3/49) and papillomas of the transitional epithelium lining the renal pelvis (0/50; 7/50; 3/49); a transitional cell carcinoma occurred in a low dose male rat. There were no tubular cell or transitional cell neoplasms of the kidney in female rats.

Hematopoietic System Effects in the Two-Year Studies: The incidence of mononuclear cell leukemia was increased in high dose male rats (10/50; 11/50; 17/50).

Genetic Toxicity: Dimethyl methylphosphonate was not mutagenic when tested in the *Salmonella typhimurium*/microsome assay by the preincubation protocol with strains TA98, TA100, TA1535, or TA1537 with or without metabolic activation. The chemical did induce forward mutations in the mouse lymphoma L5178Y/$TK^{+/-}$ assay system in the absence of metabolic activation. Treatment of cultured Chinese hamster ovary cells with dimethyl methylphosphonate did not induce chromosomal aberrations; however, sister chromatid exchanges were induced after exposure to this chemical in both the presence and absence of metabolic activation. When fed to Drosophila, dimethyl methylphosphonate induced a significant increase in the frequency of sex-linked recessive lethal mutations but did not induce reciprocal translocations. Dimethyl methylphosphonate caused a dominant lethal effect in male rats and mice.

Studies of Reproductive Effects: Dimethyl methylphosphonate caused a dose-related increase in the number of fetal resorptions in undosed female rats and mice mated with males that received the chemical by gavage in water 5 days per week for 13 weeks at doses of 0-2,000 mg/kg per day. After the 13-week dosing period, histopathologic changes were seen in the kidney and testis of male rats

but not in male mice; dosed male rats sired fewer litters and fewer pups per litter. Dose-related decreases in sperm count and sperm motility occurred in male rats but not in male mice. Toxic effects to the reproductive system of male rats and mice were reversible after a 13- to 14-week recovery period.

Data Audit: An audit of the experimental data was conducted for the 2-year studies on dimethyl methylphosphonate. No data discrepancies were found that influenced the final interpretations.

Conclusions: Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of dimethyl methylphosphonate for male F344/N rats as shown by increased incidences of tubular cell hyperplasia, tubular cell adenocarcinomas, hyperplasia of the transitional cell epithelium, and transitional cell papillomas of the kidney. There was an increased incidence of mononuclear cell leukemia in male rats at 1,000 mg/kg. Renal toxicity and decreased survival occurred in dosed male rats. There was *no evidence of carcinogenic activity* of dimethyl methylphosphonate for female F344/N rats given doses of 500 or 1,000 mg/kg. The study in male $B6C3F_1$ mice was an *inadequate study of carcinogenic activity* because of decreased survival in both dosed groups. There was *no evidence of carcinogenic activity* for female $B6C3F_1$ mice receiving dimethyl methylphosphonate at 1,000 mg/kg; decreased survival of female mice at 2,000 mg/kg made this group inadequate for determination of carcinogenic activity.

SUMMARY OF THE TWO-YEAR GAVAGE AND GENETIC TOXICOLOGY STUDIES OF DIMETHYL METHYLPHOSPHONATE

Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses			
0, 500, or 1,000 mg/kg dimethyl methylphosphonate in corn oil	0, 500, or 1,000 mg/kg dimethyl methylphosphonate in corn oil	0, 1,000, or 2,000 mg/kg dimethyl methylphosphonate in corn oil	0, 1,000, or 2,000 mg/kg dimethyl methylphosphonate in corn oil
Nonneoplastic effects			
Renal tubular cell hyperplasia; renal transitional cell hyperplasia	None	None	None
Neoplastic effects			
Renal tubular cell adenocarcinomas; renal transitional cell papillomas	None	None	None
Level of evidence of carcinogenic activity			
Some evidence	No evidence	Inadequate study	No evidence
Other considerations			
--	--	Reduced survival of dosed groups	--
Genetic toxicology			
Not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 with or without metabolic activation. Induced forward mutations in the mouse lymphoma L5178Y/TK$^{+/-}$ assay system in the absence of metabolic activation. Did not induce chromosomal aberrations in cultured CHO cells. SCEs significantly increased in both presence and absence of metabolic activation. Induced significant increase in frequency of sex-linked recessive lethal mutations in Drosophila. Caused dominant lethal effect in male rats and mice.			

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 10.

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential.

Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans.

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence including: animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results ("Clear Evidence" and "Some Evidence"); one category for uncertain findings ("Equivocal Evidence"); one category for no observable effects ("No Evidence"); and one category for experiments that because of major flaws cannot be evaluated ("Inadequate Study"). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Reports series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following quintet is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.
- **No Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenic Activity** is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. This should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- The adequacy of the experimental design and conduct;
- Occurrence of common versus uncommon neoplasia;
- Progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic lesions;
- Some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- Combining benign and malignant tumor incidences known or thought to represent stages of progression in the same organ or tissue;
- Latency in tumor induction;
- Multiplicity in site-specific neoplasia;
- Metastases;
- Supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- The presence or absence of dose relationships;
- The statistical significance of the observed tumor increase;
- The concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- Survival-adjusted analyses and false positive or false negative concerns;
- Structure-activity correlations; and
- In some cases, genetic toxicology.

These considerations together with the definitions as written should be used as composite guidelines for selecting one of the five categories. Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

> The term *chemical carcinogenesis* generally means the induction by chemicals of neoplasms not usually observed, the induction by chemicals of more neoplasms than are generally found, or the earlier induction by chemicals of neoplasms that are commonly observed. Different mechanisms may be involved in these situations. Etymologically, the term *carcinogenesis* means induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign neoplasms. In the Technical Reports, the words *tumor* and *neoplasm* are used interchangeably.

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on dimethyl methylphosphonate on August 19, 1986, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF DIMETHYL METHYLPHOSPHONATE

On August 19, 1986, the draft Technical Report on the toxicology and carcinogenesis studies of dimethyl methylphosphonate received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. J.K. Dunnick, NTP, introduced the studies by reviewing the experimental design, results, and proposed conclusions (some evidence of carcinogenic activity for male rats; no evidence of carcinogenic activity for female rats; inadequate study of carcinogenic activity for male mice; no evidence of carcinogenic activity for female mice).

Dr. Crowley, a principal reviewer, agreed with the conclusions for male and female rats and male mice. He proposed that the conclusion for female mice be changed to inadequate study of carcinogenic activity based on there being reasonable survival only in the low dose group. Dr. Popp said that since there was one valid dose group, he thought the study was adequate.

As a second principal reviewer, Dr. Purchase commented that the substantial reduction in body weight and survival in high dose male rats indicated that the dose was excessive and made the findings difficult to interpret. Regarding mononuclear cell leukemia in male rats, he said that it would be appropriate to analyze stage-1 and stage-2 (nonlethal) leukemia by the incidental tumor test and to analyze stage-3 (lethal) leukemia by the life table test. Dr. J. Haseman, NIEHS, said such analyses were done but because most of the leukemia was stage 3, this analysis gave results similar to those obtained for the life table test. Further, he noted that the kidney lesions rather than the leukemia were the primary basis for the conclusion of some evidence of carcinogenic activity in male rats.

As a third principal reviewer, Dr. Gallo agreed with the conclusions as written. He thought that there could be some expanded discussion of the hypothesis regarding chemically induced renal lesions in male rats and increased renal tubular levels of α-2-microglobulin. [See page 57.]

Dr. Crowley moved that the Technical Report on dimethyl methylphosphonate be accepted with the conclusion as written for male rats (some evidence of carcinogenic activity). Dr. Hooper seconded the motion, and it was approved unanimously with eight votes. Dr. Crowley then moved for acceptance of the conclusion as written for female rats (no evidence of carcinogenic activity) and of the conclusion as written for male mice (inadequate study of carcinogenic activity). Dr. Hooper seconded both motions, and they were approved unanimously with eight votes. Dr. Crowley moved that the conclusion for female mice, no evidence of carcinogenic activity, be changed to inadequate study of carcinogenic activity. Dr. Chinchilli seconded the motion, which failed by six votes to two (Dr. Chinchilli and Dr. Crowley). Dr. Mirer moved that the conclusion as written be amended to state that higher doses might have been tolerated. Dr. Hooper seconded that motion, which failed by seven votes to one (Dr. Mirer). Dr. Purchase moved that the conclusion for female mice be accepted as written. Dr. Popp seconded the motion, and it was approved by five reviewers with three dissenting (Dr. Chinchilli, Dr. Crowley, and Dr. Mirer).

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Dimethyl Methylphosphonate is based on the first 13-week studies that began in December 1979 and ended in March 1979, the second 13-week studies (rats) that began in August 1980 and ended in November 1980, and the 2-year studies that began in July 1981 (rats) or November 1981 (mice) and ended in July 1983 (rats) or November 1983 (mice) at Litton Bionetics, Inc.

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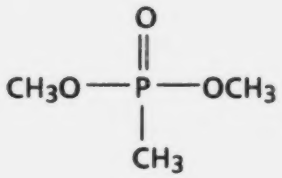
I. INTRODUCTION

Use and Production
Worker Exposure and Environmental Fate
Studies in Animals
Genetic Toxicity
Study Rationale

I. INTRODUCTION



DIMETHYL METHYLPHOSPHONATE

CAS No. 756-79-6

$C_3H_9O_3P$ Molecular weight 124.1

Synonyms: Fyrol DMMP; Methyl phosphonic acid, dimethyl ester; DMMP; Methanephosphonic acid dimethyl ester; Dimethyl methanephosphonate

Use and Production

Dimethyl methylphosphonate is used as a flame retardant (Fyrol DMMP) in epoxy resins, acrylic latexes, unsaturated polyesters, urethane coatings, urethane rigid foam, and vinyl copolymers because it is a good solvent with low viscosity. Dimethyl methylphosphonate is used as a preignition additive for gasoline, an antifoam agent, a plasticizer and stabilizer, a textile conditioner, and an antistatic agent and as an additive to solvents and low-temperature hydraulic fluids; it is also used in heavy metal extraction and solvent separation (Kirk-Othmer, 1980; USEPA, 1983a). Dimethyl methylphosphonate has been used experimentally as a nerve gas simulant to mimic the physical and spectroscopic (but not the biologic) properties of anticholinesterase agents (U.S. Naval Surface Weapons Center, 1982; Jones et al., 1948). The U.S. production range for dimethyl methylphosphonate in 1977 was 0.2-2 million pounds (91,000-910,000 kg). Dimethyl methylphosphonate is made by molecular rearrangement of trimethyl phosphite, which is catalyzed by a halogenated organic compound (USEPA, 1983a). Some properties of dimethyl methylphosphonate are summarized in Table 1.

Worker Exposure and Environmental Fate

No information is available on worker exposure to dimethyl methylphosphonate during the production process. Dimethyl methylphosphonate was identified in a liquid waste lagoon (Guzewich et al., 1983). The average half-life in soil is estimated at 12 days and in water at 1-30 weeks, depending on temperature and initial concentration (USEPA, 1983b).

Studies in Animals

The acute oral LD_{50} value is estimated at greater than 3,000 mg/kg for rats and greater than 6,000 mg/kg for mice. The compound is an irritant to the skin and eyes of rabbits (USEPA, 1983b).

Male F344/N rats and B6C3F$_1$ mice administered dimethyl methylphosphonate by gavage in water, 5 days per week for 13 weeks at doses of 0, 250, 500, 1,000, or 2,000 mg/kg, showed dose-related toxicity to the reproductive system (Dunnick et al., 1984a,b; Chapin et al., 1984); a dominant lethal effect (increased fetal resorptions) was seen after male rats and mice, dosed for 13

TABLE 1. SOME PHYSICAL PROPERTIES OF DIMETHYL METHYLPHOSPHONATE (a)

Boiling point	181° C at 754 mm Hg
Melting point	43° C
Density	1.150 g/ml at 20° C
Solubility in water	>300 mg/ml
Index of refraction (n_D)	1.4137 at 20° C
Flash point, Cleveland open cup	220° F
Fire point, Cleveland open cup	350° F
Viscosity (centistokes)	
77° F	1.81
100° F	1.48
210° F	0.84
Vapor pressure (torr)	
10°-65° C	<0.1-20

(a) USEPA, 1983b; Mobil Chemical Co.; MRI, 1982, 1986

weeks, were mated to undosed females. Decreased body weight gain and histopathologic changes (including vacuolization and necrosis of the testis and lack of spermatogenesis) were seen in male rats but not in male mice at 2,000 mg/kg. A dose-related decrease in sperm count and sperm motility was seen in male rats but not in male mice; dosed male rats sired fewer litters and fewer pups per litter than did vehicle control rats. The kidneys of dosed male rats (but not dosed male mice) had varying degrees of tubular cell regeneration, hyaline droplet degeneration, and cellular infiltrate. Toxicity to the reproductive system was reversible after a 13- to 14-week recovery period. No metabolism studies have been reported in the literature.

Hollingshaus et al. (1981) reported no delayed neurotoxicity in adult hens after daily intraperitoneal injections of dimethyl methylphosphonate at 50 mg/kg for 10 days. The NTP is currently conducting an acute neurotoxicity study of dimethyl methylphosphonate in hens, in which the chemical is administered by gavage at the LD_{50} dose.

Genetic Toxicity

Dimethyl methylphosphonate was not mutagenic in the *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 in either the presence or absence of S9 from Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver when tested in the standard plate incorporation assay (Aerospace Medical Research Laboratory, 1983) or in a preincubation protocol (Appendix E, Table E1; Mortelmans et al., 1986). Dimethyl methylphosphonate induced forward mutations in the mouse lymphoma L5178Y/$TK^{+/-}$ assay (Table E2) but not in the Chinese hamster ovary (CHO) cell/HGPRT assay (Aerospace Medical Research Laboratory, 1983); both assays were performed in the absence of S9.

In NTP studies, dimethyl methylphosphonate induced sister chromatid exchanges (SCEs) in CHO cells in the absence of S9 over a concentration range of 1.6-11 mg/ml (Table E3). No significant increases in SCEs were observed at doses up to 1 mg/ml in studies sponsored by the Air Force. SCEs were also induced in the presence of S9 from Aroclor 1254-induced male Sprague Dawley rat liver, but only in the concentration range of 11-22 mg/ml. Dimethyl methylphosphonate did not induce neoplastic transformation in the BALB/c 3T3 cell assay (Aerospace Medical Research Laboratory, 1983).

In studies performed by the United States Air Force, dimethyl methylphosphonate induced chromosomal aberrations in CHO cells at the highest concentration tested (1 mg/ml) in the absence of exogenous metabolic activation (Aerospace Medical Research Laboratory, 1983), but in NTP studies, it did not induce chromosomal aberrations either in the presence or absence of Aroclor 1254-induced Sprague Dawley rat liver S9 when tested at concentrations up to 22 mg/ml (Table E4).

When tested for mutagenicity in vivo, dimethyl methylphosphonate significantly increased the frequency of sex-linked recessive lethal mutations in the germ cells of Drosophila males fed 23,735 ppm in a 5% sucrose solution (Table E5). This procedure did not induce reciprocal translocations (Table E6). The results with Drosophila and the dominant lethal effects seen in rats and mice (Dunnick et al., 1984a,b) demonstrate that dimethyl methylphosphonate induces chromosomal damage in postmeiotic germ cells.

Study Rationale

Dimethyl methylphosphonate was nominated in 1976 by the U.S. Army for toxicology and carcinogenesis studies because it was being considered for use as an anticholinesterase agent simulant to mimic the physical and spectroscopic (but not biologic) properties of these agents. Recently, toxicology and carcinogenesis studies have been completed on the three other candidate simulants nominated for testing by the U.S. Army: tris(2-ethylhexyl)phosphate (NTP, 1984), dimethyl morpholinophosphoramidate (NTP, 1986a), and dimethyl hydrogen phosphite (NTP, 1985a). All four chemicals were administered by the same route to facilitate comparison of results. Corn oil was chosen as a common vehicle because of the potential for hydrolysis in water of some of the chemicals in the group.

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PROCUREMENT AND CHARACTERIZATION OF DIMETHYL METHYLPHOSPHONATE

Dimethyl methylphosphonate was obtained in five lots from either Edgewood Arsenal or Stauffer Chemical Company (Table 2). All lots were obtained as clear colorless liquids. Identity and purity determinations were conducted by the analytical chemistry laboratory (Midwest Research Institute, MRI). (MRI reports on the analyses performed in support of the dimethyl methylphosphonate studies are on file at NIEHS.) The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra of all lots were consistent with the spectra expected for the structure of dimethyl methylphosphonate (representative spectra presented in Figures 1 and 2). Purity of all lots studied was determined by elemental analysis, Karl Fischer water analysis, thin-layer chromatography, and gas chromatography. Thin-layer chromatography was performed with silica gel plates with iodine vapor visualization and a mobile phase of either acetone (100%) or methanol (100%). Gas chromatographic analysis was performed with flame ionization detection on either a 10% Carbowax 20M-TPA column (system 1) or a 20% SP2100/0.1% Carbowax 1500 column (system 2). Results of the purity analyses are presented in Table 3.

Stability studies with the gas chromatographic system described above for system 1 indicated that dimethyl methylphosphonate was stable as a bulk chemical when kept for 2 weeks at temperatures of up to 60° C. Further confirmation of the stability of the bulk chemical during the toxicity studies (storage at 20° C) was obtained by gas chromatographic analysis with the same column as that described above for system 2. No deterioration was seen over the course of the studies. Identity of the chemical at the study laboratory was confirmed by infrared spectroscopy.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Dimethyl methylphosphonate was mixed with corn oil as described in Table 4. Studies conducted by the study laboratory indicated that the preparation of homogeneous dose mixtures required both blending with a Polytron® mixer and mechanical stirring and that dose mixtures could be resuspended adequately by handmixing and stirring with a magnetic stirrer. The analytical chemistry laboratory conducted stability studies of dose mixtures by gas chromatography with the same column as that described above for system 1. The results of this study indicated that dimethyl methylphosphonate at 0.6% in corn oil is stable when stored at room temperature for up to 7 days. A subsequent stability study performed at the study laboratory indicated that dimethyl methylphosphonate/corn oil mixtures are stable for 14 days under refrigeration. In the 2-year studies, dose mixtures were stored at 4° C for no longer than 13 days.

TABLE 2. IDENTITY AND SOURCE OF LOTS USED IN THE GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE

Single-Administration Studies	Fifteen-Day Studies	First Thirteen-Week Studies	Second Thirteen-Week Studies	Two-Year Studies
Lot Numbers				
EA113077	EA113077	EA113077	4182-2	4182-2; L120381; 1114L-6-1; 1114L-2-1
Date of Initial Use				
8/2/78	Rats--8/31/78; mice--9/18/78	12/29/78 (1/8/79 for the 8,000 mg/kg mice)	8/29/80	4182-2, 7/16/81; L120381, 1/82; 1114L-6-1, 9/82; 1114L-2-1, 10/83
Supplier				
Edgewood Arsenal, Aberdeen Proving Ground, Aberdeen, MD	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies; or Stauffer Chemical Co., Westport, CT (lot nos. 11146L-6-1 and 1114L-2-1)

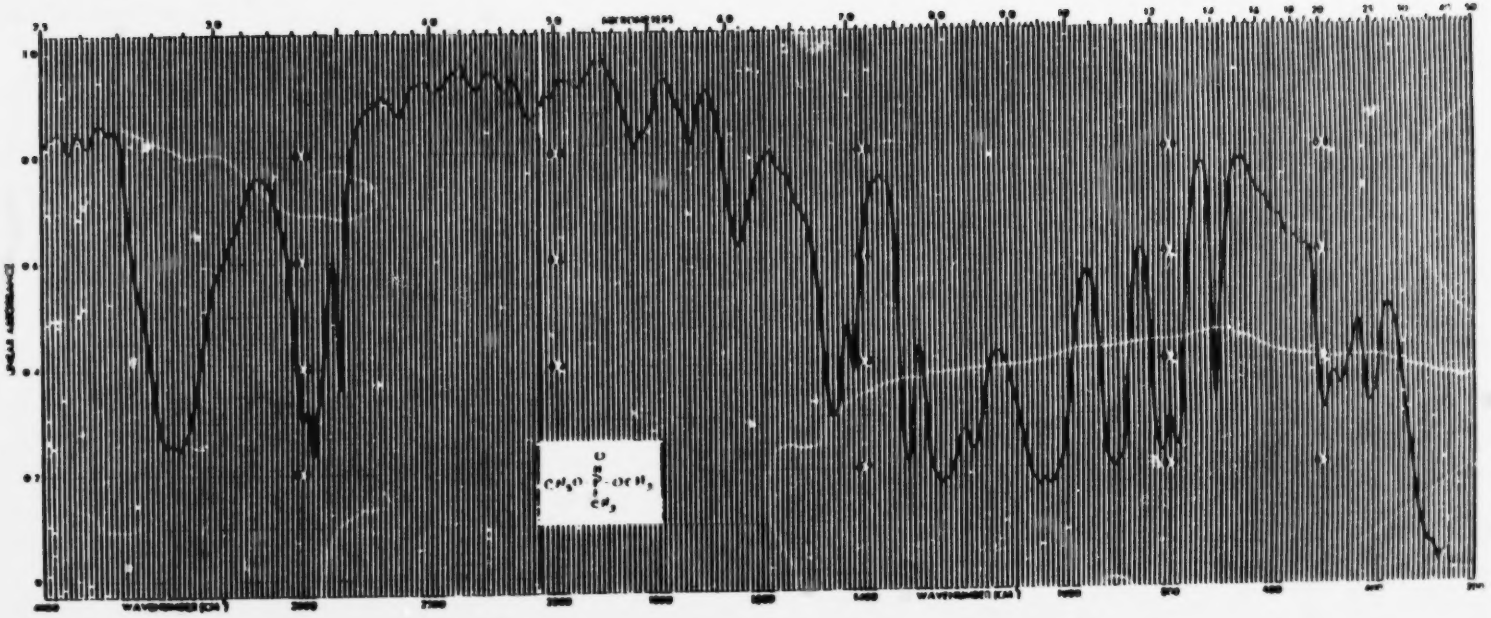

FIGURE 1. INFRARED ABSORPTION SPECTRUM OF DIMETHYL METHYLPHOSPHONATE (LOT NO. 1114L-6-1)

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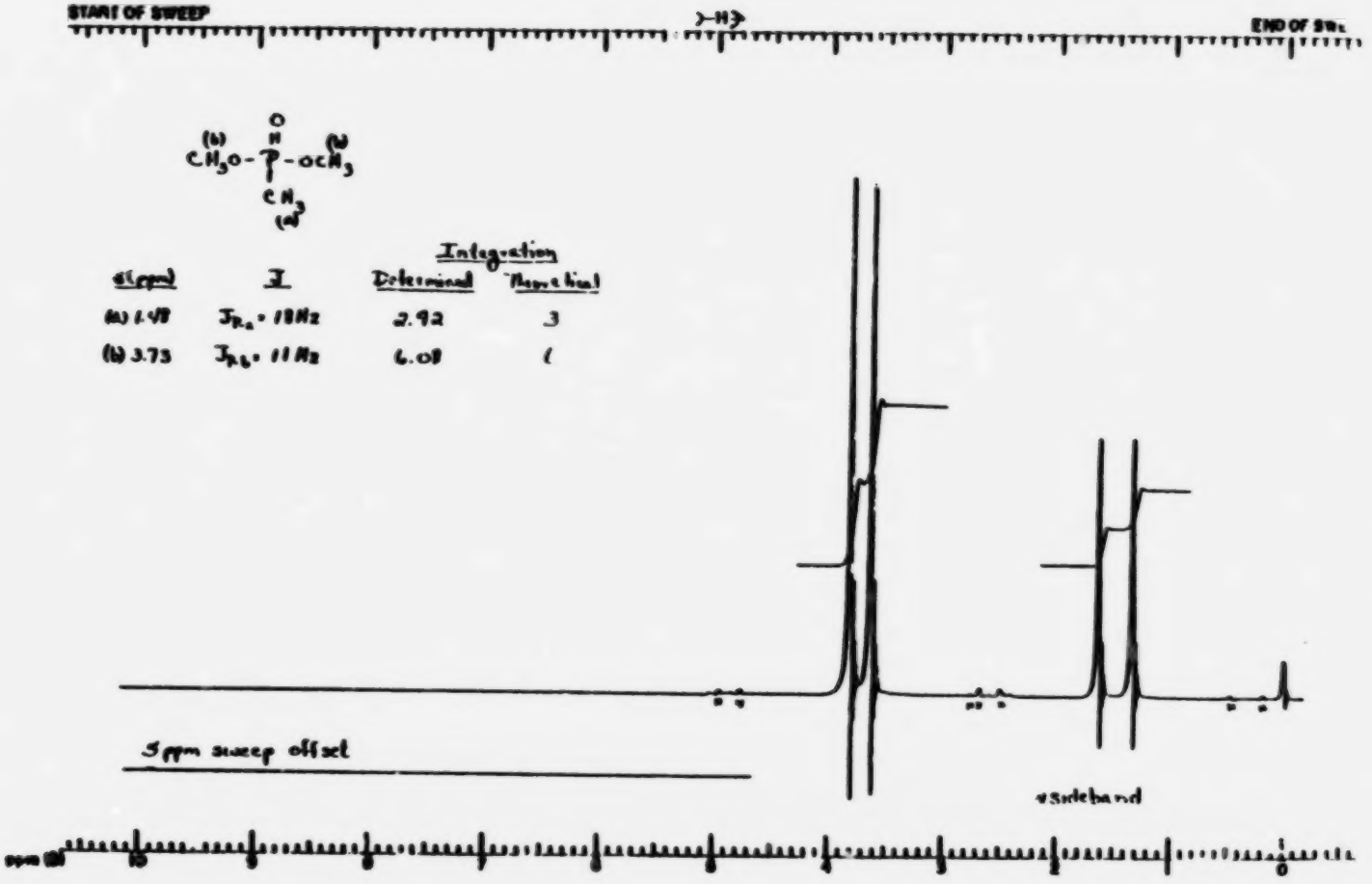

FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF DIMETHYL METHYLPHOSPHONATE (LOT NO. 1114L-6-1)

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TABLE 3. RESULTS OF PURITY ANALYSIS OF LOTS USED IN THE GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE

Lot Number	Determined Purity (percent)	Percent Water	Percent Total Impurities	
			System 1 (a)	System 2 (b)
EA1!3077	>98	0.11	1.5	0.5
4182-2	~98	0.25	1.35	2.01
1114L-6-1	>99	0.04	0.48	0.47
1114L-2-1	~99	0.06	1.1	1.1

(a) A 10% Carbowax 20M-TPA column
(b) A 20% SP2100/0.1% Carbowax 1500 column

TABLE 4. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE

Single-Administration Studies	Fifteen-Day Studies	First Thirteen-Week Studies	Second Thirteen-Week Studies	Two-Year Studies
Preparation				
Agitated in test tube; mixed for 2 min with stirring bar	Dimethyl methylphosphonate mixed with corn oil for 22 min with a vortex mixer and resuspended before dosing	Mixed in a graduated cylinder by inversion	Appropriate amount of corn oil added to dimethyl methylphosphonate; each dose mixture homogenized with a Polytron® mixer for at least 2 min at medium-high speed and then placed in five separate vials, one for each dose day of the week. Dose mixtures rehomogenized for 1 min with the Polytron® no more than 1 h before dosing. In animal room, each mixture stirred continuously with a magnetic stirrer throughout the dosing period to prevent separation.	Dimethyl methylphosphonate formulated with corn oil with a Polytron® mixer and resuspended daily with a magnetic stirrer
Maximum Storage Time				
N/A	7 d	1 wk	1 wk	13 d
Storage Conditions				
N/A	4°C	4°C	4°C	4°C

Periodic analysis of dimethyl methylphosphonate/corn oil dose mixtures were conducted at the study laboratory and the analytical chemistry laboratory by methanolic extraction of the dose mixtures followed by gas chromatographic analysis of the resultant extract with system 1. Dose mixtures were analyzed once during the second 13-week studies. The results ranged from 100% to 105% of the target concentration (Table 5).

During the 2-year studies, the dose preparations were analyzed at approximately 8-week intervals. Because 44/47 mixtures analyzed were within ±10% of the target concentration, it is estimated that the dose mixtures were prepared within specifications 94% of the time (Table 6). The three dose formulations determined to be out of specifications were within ±13% of the target concentrations. Referee analysis was periodically performed by the analytical chemistry laboratory. Generally, good agreement was found between the results at the two laboratories (Table 7).

Deaths occurred after dosing in September 1982 in high dose mice and in April 1983 in low dose male mice. As a result, special analyses were performed on the contents of the dosing containers and their corresponding archive samples. The concentrations in the archive samples were within the specified limits, whereas that of the high-dose sample taken in the animal room was high (134% of target), and the low-dose sample taken in the animal room was low (79% of target). Because the archive samples were determined to be within specifications, it would appear that a dosing accident or misdosing due to improper handling or resuspending of the dose mixture occurred in the animal room on these days.

TABLE 5. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE SECOND THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml) (a)	Determined as a Percent of Target
08/28/80	0	0	--
	38.4	40.2	105
	77.0	77.9	101
	153.8	154	100
	307.5	307	99.8
	615.0	632	103

(a) Results of duplicate analysis

TABLE 6. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE

Date Mixed	Concentration of Dimethyl Methylphosphonate in Corn Oil (a) for Target Concentration (mg/ml)		
	76.9	153.8	307.7
07/08/81	70.7	(b) 204	285
07/09/81	--	(c) 155	--
07/15/81	75.4	139	292
07/15/81 (d)	75.7	152	306
09/02/81	78.4	149	301
10/28/81	75.2	146	--
11/18/81	75.9	148	296
11/24/81	76.1	152	296
11/24/81 (d)	76.0	151	294
01/13/82	74.1	141	289
03/10/82	76.3	142	291
05/05/82	69.1	(b) 136	278
05/05/82 (d)	72.7	--	247
05/11/82	--	(c) 142	--
05/11/82 (d)	--	148	--
06/30/82	74.3	151	281
08/25/82	76.4	149	(b) 274
08/27/82	--	--	(c) 287
09/29/82	--	--	312
09/29/82 (d)	--	--	(e) 411
10/20/82	77.6	150	302
10/20/82 (d)	77.3	153	307
12/16/82	75.3	148	301
02/09/83	78.4	156	302
04/06/83	74.1	152	293
04/06/83 (d)	70.4	150	292
04/29/83	--	143	--
04/29/83 (d)	--	(f) 121	--
06/01/83	72.7	147	292
07/27/83	--	144	291
09/21/83	--	141	294
09/21/83 (d)	--	153	331
Mean (mg/ml)	75.1	149	293
Standard deviation	2.57	14.2	9.4
Coefficient of variation (percent)	3.4	9.5	3.2
Range (mg/ml)	69.1-78.4	136-204	274-312
Number of samples	16	19	18

(a) Results of duplicate analysis
(b) Out of specifications; not used in study.
(c) Remix; not included in the mean.
(d) Analysis of animal room samples; samples taken during dosing; not included in the mean.
(e) Animal room sample; out of specifications; corresponds to deaths in high dose mice at week 45.
(f) Animal room sample; out of specifications; corresponds to death in low dose male mice at week 77.

TABLE 7. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
07/08/81	307.7	285	(c) 245
05/05/82	76.9	69.1	69.8
10/20/82	153.8	150	144
02/09/83	153.8	156	144
09/21/83	307.7	294	280

(a) Results of duplicate analysis
(b) Results of triplicate analysis
(c) The 16% difference in results between the study laboratory and the referee laboratory was attributed to possible differences in resuspension techniques.

II. MATERIALS AND METHODS

SINGLE-ADMINISTRATION STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 14 days before the studies began. Animals were 6 weeks old when placed on study. Groups of five males and five females were fasted and then administered a single dose of 1,470, 2,150, 3,160, 4,640, or 6,810 mg/kg dimethyl methylphosphonate in corn oil by gavage. Rats and mice were observed daily. A necropsy was performed on all animals that died before the end of the studies. Details of animal maintenance are presented in Table 8.

FIFTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 16 days (rats) or 18 days (mice) before the studies began. Rats were 6 weeks old when placed on study. Groups of five males and five females of each species were administered 0, 1,250, 2,500, 5,000, 10,000, or 15,000 mg/kg dimethyl methylphosphonate in corn oil by gavage for 15 consecutive days. The 15,000 mg/kg dose for mice was administered neat. Rats and mice were observed twice per day and were weighed on day 0, and mice were weighed also on day 15. A necropsy was performed on all animals. Stomachs of mice were examined microscopically. Details of animal maintenance are presented in Table 8.

FIRST THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of dimethyl methylphosphonate and to determine the doses to be used in the 2-year studies.

Five- to six-week-old male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 16 days, and assigned to groups according to a series of tables of random numbers. Groups of 10 rats and 10 mice of each sex were administered 0, 250, 500, 1,000, 2,000, or 8,000 mg/kg dimethyl methylphosphonate, 5 days per week for 13 weeks. The 8,000 mg/kg group of mice had only seven males and six females. The original report does not explain the discrepancy in the number of animals, but it may have been due to a shortage of animals. The 250 mg/kg groups of rats and the 8,000 mg/kg groups of mice were started 1-2 weeks after the other groups.

Animals were housed five per cage. Feed and water were available ad libitum. Animals were checked two times per day; moribund animals were killed. Individual animal weights were recorded weekly.

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 8.

SECOND THIRTEEN-WEEK STUDIES

Thirteen-week studies in rats were repeated because of gavage accidents in the lower dose groups in the first 13-week studies.

Five- to six-week old male and female F344/N rats were obtained from Charles River Breeding Laboratories, observed for 16 days, and assigned to groups according to a table of random numbers. Groups of 10 rats of each sex were administered 0, 250, 500, 1,000, 2,000, or 4,000 mg/kg dimethyl methylphosphonate, 5 days per week for 13 weeks.

Animals were housed five per cage. Feed and water were available ad libitum. Animals were checked two times per day; moribund animals were killed. Individual animal weights were recorded weekly.

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Liver weights were taken, and liver weight to body weight ratios were calculated. Tissues and groups examined are listed in Table 8.

TABLE 8. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE

Single-Administration Studies	Fifteen-Day Studies	First Thirteen-Week Studies	Second Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN				
Size of Study Groups				
5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species (high dose mice--7 males and 6 females)	10 males and 10 females (rats only)	50 males and 50 females of each species
Doses				
1,470, 2,150, 3,160, 4,640, or 6,810 mg/kg dimethyl methylphosphonate in corn oil by gavage	0, 1,250, 2,500, 5,000, 10,000, or 15,000 mg/kg dimethyl methylphosphonate in corn oil by gavage (15,000 mg/kg dose administered neat)	0, 250, 500, 1,000, 2,000, 4,000, or 8,000 mg/kg dimethyl methylphosphonate in corn oil by gavage; dose vol--rats: 6.5 ml/kg during wk 1 (double the intended dose); from wk 2, dose vol--3.33 ml/kg, except for the 8,000 mg/kg group: 6.5 ml/kg; mice: 3.3 ml/kg 12/29/78-1/5/79, then 6.5 ml/kg after 1/8/79	0, 250, 500, 1,000, 2,000, or 4,000 mg/kg dimethyl methylphosphonate in corn oil by gavage; dose vol--6.5 ml/kg	Rats--0, 500, or 1,000 mg/kg dimethyl methylphosphonate in corn oil by gavage; dose vol--6.5 ml/kg; mice--0, 1,000, or 2,000 mg/kg dimethyl methylphosphonate in corn oil by gavage; dose vol--6.5 ml/kg
Date of First Dose				
8/2/78	Rats--8/31/78; mice--9/18/78	Rats--12/29/78 (250 mg/kg group started at week 2); mice--12/29/78 (1/8/79 for the 8,000 mg/kg group)	8/29/80	Rats--7/16/81; mice--11/24/81
Date of Last Dose				
N/A	Rats--9/14/78; mice--10/2/78	3/28/79	11/28/80	Rats--7/11/83; mice--11/18/83
Duration of Dosing				
Single dose only	15 consecutive d	5 d/wk for 12 or 13 wk	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation				
Observed immediately after dosing, at 1 h and 4 h, and 1 × d for 14 d	Rats--observed 2 × d; weighed on d 0; mice--observed 2 × d; weighed on d 0 and d 15	Observed 2 × d; weighed 1 × wk	Same as first 13-wk studies	Observed 2 × d; palpated 1 × 4 wk; weighed 1 × wk for 13 wk, 1 × 4 wk thereafter
Necropsy and Histologic Examination				
Necropsy performed on all animals that died during the studies	Necropsy performed on all animals; histologic exam of the stomach performed on all mice	Necropsy performed on all animals. Histologic exam performed on all animals that died before the end of the studies, on vehicle controls, on highest dose groups of rats, and on two highest dose groups of mice; tissues examined include: adrenal glands, brain, colon, esophagus, eyes (if grossly abnormal), gallbladder (mice), gross lesions and tissue masses, heart, kidneys, liver, lungs and mainstem bronchi, mammary	Same as first 13-wk studies	Necropsy and histologic exam performed on all animals; the following tissues were examined: adrenal glands, brain, cecum, colon, costochondral junction, duodenum, esophagus, eyes, gallbladder (mice), gross lesions and tissue masses, heart, ileum, jejunum, kidneys, larynx, liver, lungs and mainstem bronchi, mammary gland, mandibular and mesenteric lymph nodes, nasal cavity, pancreas, parathyroids, pituitary gland,

TABLE 8. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE (Continued)

Single-Administration Studies	Fifteen-Day Studies	First Thirteen-Week Studies	Second Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN (Continued)				
		gland, mandibular or mesenteric lymph node, pancreas, parathyroids, pituitary gland, prostate/testes or ovaries/uterus, regional lymph nodes, salivary glands, skin, small intestine, spinal cord (if neurologic signs present), spleen, sternebrae or femur or vertebrae including marrow, stomach, thymus, thyroid gland, trachea, and urinary bladder; tissues examined for other groups of rats: kidneys, salivary glands, and testes.		prostate/testes/seminal vesicles or ovaries/uterus, rectum, regional lymph nodes, salivary glands, sciatic nerve, skin, spinal cord, spleen, sternum including marrow, stomach, thyroid gland, thigh muscle, thymus, trachea, and urinary bladder.
ANIMALS AND ANIMAL MAINTENANCE				
Strain and Species				
F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats	F344/N rats; $B6C3F_1$ mice
Animal Source				
Charles River Breeding Laboratories (Portage, MI)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies	Frederick Cancer Research Center (Frederick, MD)
Study Laboratory				
Litton Bionetics, Inc.	Litton Bionetics, Inc.	Litton Bionetics, Inc.	Litton Bionetics, Inc.	Litton Bionetics, Inc.
Method of Animal Identification				
Ear punch	Ear notch	Rats--ear tag; mice--ear punch, toe clip	Ear tag	Same as first 13-wk studies
Time Held Before Study				
14 d	Rats--16 d; mice--18 d	16 d	16 d	20 d
Age When Placed on Study				
6 wk	Rats--6 wk; mice--not available	7-8 wk	7-8 wk	Rats--male, 8 wk; female, 7 wk; mice--8 wk
Age When Killed				
8 wk	Rats--8 wk; mice--not available	21-22 wk	21-22 wk	Rats--113 wk; mice--112-113 wk
Necropsy Dates				
8/16/78	Rats--9/15/78; mice--10/3/78	Rats--4/3/79-4/4/79; mice--3/30/79-4/4/79	12/1/80-12/2/80	Rats--7/19/83-7/20/83; mice--11/28/83-11/29/83
Method of Animal Distribution				
Assigned to cages such that cage weights were approximately equal for each sex and species	Same as single-administration studies	Assigned to groups according to a series of tables of random numbers	Same as first 13-wk studies	Randomized to cages by one table of random numbers, then to groups by another table

TABLE 8. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE (Continued)

Single-Administration Studies	Fifteen-Day Studies	First Thirteen-Week Studies	Second Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)				
Feed				
Purina Lab Chow® meal (Ralston Purina Co., St. Louis, MO); available ad libitum	Same as single-administration studies	Purina Lab Chow® pellets (Ralston Purina Co., St. Louis, MO); available ad libitum	NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as second 13-wk studies
Bedding				
Absorb-Dri® (Lab Products, Garfield, NJ)	Same as single-administration studies	Same as single-administration studies	Absorb-Dri® (Lab Products, Inc., Gaithersburg, MD)	Rats--Absorb-Dri® heat-treated hardwood chips (Lab Products, Inc., Gaithersburg, MD) used until 9/23/81; Sani-Chips®, hardwood chip animal bedding (P.J. Murphy Forest Products Corp., Rochelle Park, NJ) used thereafter; mice--Sani-Chips® (P.J. Murphy Forest Products Corp., Rochelle Park, NJ)
Water				
Acidified to pH 2.5; available ad libitum in bottles	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cages				
Polycarbonate (Lab Products, Inc., Garfield, NJ, and Rochelle Park, NJ)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies	Polycarbonate (Lab Products, Inc., Garfield, NJ, and Hazleton Systems, Aberdeen, MD)
Cage Filters				
Nonwoven polyester (Snow Filtration, Cincinnati, OH)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Animals per Cage				
5	5	5	5	5
Other Chemicals on Study in the Same Room				
None	Dimethyl hydrogen phosphite	None	None	None
Animal Room Environment				
Not available	Temp--22.2°-24.4° C; hum--30%-70%; fluorescent light 12 h/d; 12-15 room air changes/h	Temp--22.2°-24.4° C; hum--30%-70%; light 12 h/d; 15 room air changes/h	Same as first 13-wk studies except 12-15 room air changes/h	Temp--usually 22.2°-24.4° C; hum--30%-70%; fluorescent light 12 h/d; 12-15 room air changes/h

II. MATERIALS AND METHODS

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were administered 0, 500, or 1,000 mg/kg dimethyl methylphosphonate in corn oil by gavage, 5 days per week for 103 weeks. Groups of 50 mice of each sex were administered 0, 1,000, or 2,000 mg/kg dimethyl methylphosphonate on the same schedule. The mouse studies were started 4 months after the rat studies because the first 2-year mouse studies were terminated after 2 months due to the large number of deaths that were related to gavage technique.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female, × C3H/HeN MTV$^-$, male) mice used in these studies were produced under strict barrier conditions at Frederick Cancer Research Center under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Animals were shipped to the study laboratory at 4-5 weeks of age and were quarantined for 20 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. Male rats and mice of each sex were placed on study at 8 weeks of age, and female rats at 7 weeks of age. The health of the animals was monitored during the course of the study according to the protocols of the NTP Sentinel Animal Program (Appendix F).

Animal Maintenance

Animals were housed five per cage; neither the cages nor racks were rotated during the studies. Cages for each dose group were arranged in columns on the rack. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 8.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 13 weeks of the studies and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead, unless they were excessively autolyzed, cannibalized, missexed, or found missing. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 8.

When the pathology evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

Representative slides selected by the Chairperson were reviewed by the PWG, which includes the laboratory pathologist, without knowledge of previously rendered diagnoses. When the

consensus diagnosis of the PWG differed from that of the laboratory pathologist, the laboratory pathologist was asked to reconsider the original diagnosis. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Slides/tissues are generally not evaluated in a blind fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle or unless there is an inconsistent diagnosis of lesions by the laboratory pathologist. Nonneoplastic lesions are not examined routinely by the quality assessment pathologist or PWG unless they are considered part of the toxic effect of the chemical.

Statistical Methods

Data Recording: Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found dead of other than natural causes or were found to be missing; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence: Three statistical methods are used to analyze tumor incidence data. The two that adjust for intercurrent mortality employ the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high dose and low dose groups with vehicle controls and tests for overall dose-response trends.

For studies in which compound administration has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. Continuity-corrected tests are used in the analysis of tumor incidence, and reported P values are one-sided.

Life Table Analyses--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and vehicle control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of

Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

Incidental Tumor Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and vehicle control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals actually examined for tumors during the time interval. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

Unadjusted Analyses--Primarily, survival-adjusted methods are used to evaluate tumor incidence. In addition, the results of the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendixes containing the analyses of primary tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

Historical Control Data: Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of tumor incidence. Consequently, control tumor incidences from the NTP historical control data base (Haseman et al., 1984, 1985) are included for those tumors appearing to show compound-related effects.

III. RESULTS

RATS

SINGLE-ADMINISTRATION STUDIES

FIFTEEN-DAY STUDIES

FIRST THIRTEEN-WEEK STUDIES

SECOND THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SINGLE-ADMINISTRATION STUDIES

FIFTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

III. RESULTS: RATS

SINGLE-ADMINISTRATION STUDIES

No compound-related deaths occurred at doses up to 6,810 mg/kg. Compound-related clinical signs were observed in all but the lowest dose groups and included transitory (1-4 hours after dosing) inactivity, unsteady gait, and prostration.

Because of a lack of dose-related mortality in the single-administration studies, doses selected for the 15-day studies were 0, 1,250, 2,500, 5,000, 10,000, and 15,000 mg/kg.

FIFTEEN-DAY STUDIES

All rats that received 10,000 or 15,000 mg/kg dimethyl methylphosphonate and 4/5 male and 4/5 female rats that received 5,000 mg/kg died before the end of the studies (Table 9). No compound-related gross pathologic effects were reported. Dosed rats that received 2,500 mg/kg or more were inactive after dosing; dosed animals at 5,000 and 10,000 mg/kg had an unsteady gait.

Doses selected for the 13-week studies were 0, 250, 500, 1,000, 2,000, 4,000, and 8,000 mg/kg because of the mortality at 10,000 and 15,000 mg/kg. Even though mortality occurred at 5,000 mg/kg in the 15-day studies, 8,000 mg/kg was selected as the high dose so that rats and mice would be administered the same doses in the 13-week studies.

FIRST THIRTEEN-WEEK STUDIES

All rats that received 8,000 mg/kg dimethyl methylphosphonate died before the end of the studies (Table 10). The final mean body weight of rats that received 4,000 mg/kg was more than 10% lower than that of the vehicle controls. Animals at 8,000 mg/kg had rough hair coats and decreased activity; decreased activity was observed by week 10 in 4,000 mg/kg males and females.

Lesions were seen in the kidney, testis, epididymus, or salivary gland (Table 11). Degeneration and atrophy of the testis (minimal severity) were observed in dosed male rats. The incidence and severity of the testicular atrophy were approximately the same in the three lowest dose groups. Degeneration of the epididymus was minimal or mild. A mild to moderate nephrosis of the kidney, characterized by hypertrophy and vacuolation of the proximal and distal tubular epithelium with accumulation of a finely granular proteinaceous material in the lumens, was seen at 8,000 mg/kg.

The 13-week studies were repeated because the deaths attributed to gavage error in lower dose groups prevented accurate dose selection for the 2-year studies. The doses selected for the second 13-week studies in rats were 0, 250, 500, 1,000, 2,000, and 4,000 mg/kg because all rats in the 8,000 mg/kg group died in the first 13-week studies.

TABLE 9. SURVIVAL OF RATS IN THE FIFTEEN-DAY GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE

Male		Female	
Dose (mg/kg)	Survival (a)	Dose (mg/kg)	Survival (a)
0	5/5	0	5/5
1,250	(b) 4/5	1,250	5/5
2,500	5/5	2,500	5/5
5,000	(c) 1/5	5,000	(d) 1/5
10,000	(e) 0/5	10,000	(f) 0/5
15,000	(g) 0/5	15,000	(g) 0/5

(a) Number surviving/number in group
(b) Day of death: 2 (probable gavage accident)
(c) Day of death: all 12
(d) Day of death: all 14
(e) Day of death: 1,7,9,9,9
(f) Day of death: 3,9,9,12,12
(g) Day of death: all 1

TABLE 10. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FIRST THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	173	311	+138	--
250	10/10	(c)	307	--	98.7
500	10/10	181	304	+123	97.7
1,000	10/10	174	295	+121	94.9
2,000	(d) 3/10	176	295	+119	94.9
4,000	(e) 8/10	168	252	+84	81.0
8,000	(f) 0/10	176	(g)	(g)	(g)
FEMALE					
0	10/10	133	194	+61	--
250	10/10	(c)	192	--	99.0
500	10/10	132	194	+62	100.0
1,000	(h) 8/10	134	188	+54	96.9
2,000	(i) 7/10	129	183	+54	94.3
4,000	(j) 3/10	130	172	+42	88.7
8,000	(k) 0/10	127	(g)	(g)	(g)

(a) Number surviving/number in group
(b) Initial group mean body weight
(c) Initial body weight not recorded
(d) Week of death: 6,9,9,9,10,11,12; 6/7 deaths attributed to gavage accidents.
(e) Week of death: 7,10
(f) Week of death: 1,1,1,1,1,1,1,1,2,5
(g) No data are reported due to the 100% mortality in this group.
(h) Week of death: 5,10; deaths attributed to gavage accidents.
(i) Week of death: 9,9,10
(j) Week of death: 1,2,2,7,9,9,9
(k) Week of death: 1,1,2,2,2,2,2,3,4,5

TABLE 11. INCIDENCES OF RATS WITH SELECTED LESIONS IN THE FIRST THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE

Site/Lesion	Vehicle Control	250 mg/kg	500 mg/kg	1,000 mg/kg	2,000 mg/kg	4,000 mg/kg	8,000 mg/kg
MALE							
Kidney nephrosis	0/10	(a)	(a)	(a)	0/10	0/10	(b) 4/10
Testis							
Atrophy	0/10	1/10	2/10	2/10	3/9	10/10	(b) 2/9
Degeneration	0/10	0/10	0/10	0/10	0/9	0/10	(b) 2/9
Epididymus							
Degeneration	0/10	0/10	0/10	0/10	0/10	9/10	(b) 3/9
Salivary gland							
Atrophy	0/10	(a)	(a)	(a)	0/10	0/10	(b) 6/10
FEMALE							
Salivary gland							
Atrophy	0/10	(a)	(a)	0/2	0/10	0/10	4/10

(a) Not examined
(b) Nine of 10 rats dead by week 2; 10th rat dead by week 5.

SECOND THIRTEEN-WEEK STUDIES

All rats that received 4,000 mg/kg and 6/10 males and 3/10 females that received 2,000 mg/kg died before the end of the studies (Table 12). Final mean body weights of rats that received 2,000 mg/kg were 6% lower than that of the vehicle controls for males and 7% lower for females. No compound-related clinical signs were seen. The liver weight to body weight ratios were significantly increased ($P<0.01$) for rats that received 2,000 mg/kg compared with those of the vehicle controls (Table 13).

Kidney lesions characteristic of spontaneous progressive nephropathy were seen in all groups of male rats (Table 14). Although the incidences of this lesion (diagnosed as nephrosis) were greater in all dosed groups except that receiving 4,000 mg/kg, the severity of the lesions in dosed and vehicle control rats was similar. Accumulation of hyaline droplets in the cytoplasm of epithelial cells was observed in convoluted tubules of the renal cortex in all dosed groups of male rats. At the time of this study, these lesions were not considered to be life threatening.

Hypospermatogenic tubules (minimal to mild) were seen in the testis of dosed male rats in the higher dose groups. The severity of the lesion was not increased with increasing dose of chemical.

Inflammation of the salivary gland, suggestive of viral sialodacryoadenitis, was seen in some high dose male and female rats.

Dose Selection Rationale: Based on the incidence of deaths and weight gain depression observed in both 13-week studies, doses selected for the 2-year studies in rats were 500 and 1,000 mg/kg dimethyl methylphosphonate, administered in corn oil by gavage, 5 days per week for 103 weeks. The kidney lesions were not considered to be life threatening.

TABLE 12. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SECOND THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	125 ± 3	340 ± 5	+215 ± 4	--
250	10/10	123 ± 4	324 ± 14	+201 ± 12	95
500	10/10	121 ± 4	336 ± 12	+215 ± 10	99
1,000	10/10	126 ± 3	336 ± 4	+210 ± 4	99
2,000	(d) 4/10	126 ± 4	321 ± 15	+190 ± 10	94
4,000	(e) 0/10	126 ± 3	(f)	(f)	(f)
FEMALE					
0	10/10	104 ± 1	197 ± 3	+93 ± 2	--
250	(e) 9/10	104 ± 3	194 ± 6	+89 ± 5	98
500	10/10	105 ± 3	205 ± 6	+100 ± 4	104
1,000	(e) 9/10	100 ± 2	190 ± 6	+91 ± 5	96
2,000	(g) 7/10	105 ± 2	184 ± 2	+77 ± 2	93
4,000	(e) 0/10	103 ± 2	(f)	(f)	(f)

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 7,7,11,12,13,13
(e) Week of death: 1
(f) No data are reported due to the 100% mortality in this group.
(g) Week of death: 1,6,10

TABLE 13. ABSOLUTE AND RELATIVE LIVER WEIGHTS OF RATS IN THE SECOND THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE (a)

Dose (mg/kg)	No. of Animals Examined	Necropsy Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Body Weight (mg/g)
MALE				
0	(b) 9	329 ± 17	11,165 ± 1,485	33.3 ± 3.99
250	10	310 ± 40	10,425 ± 1,432	33.7 ± 3.21
500	10	321 ± 34	11,721 ± 2,060	36.3 ± 4.21
1,000	10	322 ± 13	11,718 ± 1,396	36.4 ± 3.69
2,000	4	306 ± 30	(c) 13,990 ± 2,767	(d) 45.7 ± 7.98
FEMALE				
0	(e) 9	187 ± 11	5,845 ± 1,119	31.1 ± 4.87
250	9	187 ± 22	6,476 ± 1,009	34.5 ± 2.85
500	10	195 ± 17	6,450 ± 742	33.1 ± 3.20
1,000	9	179 ± 17	6,048 ± 517	34.0 ± 2.27
2,000	7	176 ± 6	6,519 ± 779	(d) 37.0 ± 4.20

(a) Mean ± standard deviation; P values are versus the vehicle controls by Dunnett's test (Dunnett, 1955).
(b) Ten livers examined; one body weight not recorded.
(c) $P<0.05$
(d) $P<0.01$
(e) Ten body weights; one liver weight not recorded.

TABLE 14. INCIDENCES OF RATS WITH SELECTED LESIONS IN THE SECOND THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE

Site/Lesion	Vehicle Control	250 mg/kg	500 mg/kg	1,000 mg/kg	2,000 mg/kg	4,000 mg/kg
MALE						
Kidney						
Nephrosis	2/10	9/10	10/10	10/10	5/9	0/10
Hyaline droplet degeneration	0/10	8/10	10/10	10/10	4/9	3/10
Hemorrhage	0/10	0/10	0/10	0/10	1/9	2/10
Testis						
Hypospermatogenesis	0/10	1/10	0/10	2/10	4/9	1/10
Giant cell degeneration	0/10	0/10	0/10	1/10	0/9	0/10
Salivary gland						
Acute inflammation	0/10	(a)	(a)	0/10	0/10	2/10
FEMALE						
Salivary gland						
Acute inflammation	0/10	(a)	(a)	(a)	1/10	1/10

(a) Not examined

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were 5%-10% lower than those of the vehicle controls between weeks 28 and 76 and 10%-24% lower between weeks 80 and 104 (Table 15 and Figure 3). Mean body weights of high dose female rats were 8%-12% lower than those of the vehicle controls after week 80. Mean body weights of low dose male and female rats were comparable to those of the vehicle controls throughout most of the studies. No compound-related clinical signs were recorded.

TABLE 15. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	500 mg/kg Av. Wt. (grams)	500 mg/kg Wt. (percent of veh. controls)	500 mg/kg No. of Survivors	1,000 mg/kg Av. Wt. (grams)	1,000 mg/kg Wt. (percent of veh. controls)	1,000 mg/kg No. of Survivors
MALE								
0	163	50	162	99	50	158	97	50
1	194	50	194	100	50	194	100	50
2	222	50	219	99	50	219	99	50
3	244	50	241	99	50	239	98	50
4	261	50	258	99	50	256	98	50
5	278	50	272	98	50	269	97	50
6	289	50	285	99	50	283	98	50
7	298	50	295	99	50	289	97	50
8	310	50	303	98	50	300	97	50
9	311	50	305	98	50	302	97	50
10	325	50	319	98	50	314	97	50
11	335	50	333	99	50	327	98	50
12	343	50	341	99	50	333	97	50
13	348	50	346	99	50	341	98	50
16	371	50	369	99	50	357	96	50
20	391	50	387	99	50	370	95	50
24	410	50	408	100	50	392	96	49
28	424	50	419	99	50	402	95	49
32	426	50	430	99	50	413	95	49
36	439	49	437	100	50	417	95	49
40	450	49	439	98	50	418	93	49
44	456	49	448	98	49	425	93	49
48	464	49	455	98	49	428	92	49
52	467	48	463	99	48	435	93	49
56	475	47	468	99	45	438	95	46
60	484	43	472	98	41	445	92	43
64	487	42	478	98	39	450	92	43
68	485	40	480	99	38	445	92	40
72	488	40	478	98	37	439	90	37
76	487	39	478	98	34	437	90	35
80	489	39	477	98	32	434	89	27
84	484	38	471	97	30	423	87	24
88	479	37	466	97	25	413	86	17
92	480	36	468	98	24	406	85	10
96	473	35	457	97	23	386	82	10
100	468	29	450	96	19	369	79	8
104	451	27	416	92	17	343	76	4
FEMALE								
0	119	50	126	106	50	123	103	50
1	134	50	141	105	50	136	101	50
2	145	50	151	104	50	149	103	50
3	153	50	158	103	50	156	102	50
4	163	50	167	102	50	163	100	50
5	168	50	173	103	50	170	101	50
6	174	50	178	102	50	173	99	50
7	176	50	181	103	50	176	100	50
8	179	50	185	103	50	178	99	50
9	181	50	188	103	50	182	101	50
10	185	50	191	103	50	187	101	50
11	188	50	193	103	50	189	101	50
12	192	50	195	102	50	192	100	50
13	193	50	198	103	50	193	100	50
16	200	50	202	101	50	198	99	50
20	206	50	209	101	50	204	99	50
24	213	50	214	100	50	208	98	50
28	219	50	218	100	50	215	98	50
32	227	50	225	99	50	223	98	50
36	229	50	225	98	50	223	97	50
40	231	50	227	98	50	226	98	49
44	238	50	231	97	50	230	97	49
48	245	49	236	96	50	235	96	49
52	254	49	247	97	50	245	96	49
56	262	49	254	97	49	252	96	45
60	266	49	258	97	48	254	95	42
64	276	49	269	97	48	265	96	42
68	283	49	276	98	45	274	97	40
72	291	48	283	97	44	277	95	40
76	298	48	286	96	44	285	96	37
80	303	47	287	95	44	278	92	30
84	304	46	294	97	44	276	91	29
88	306	44	293	96	44	283	92	27
92	310	43	301	97	42	283	91	26
96	313	37	296	95	39	281	90	26
100	314	34	293	93	35	283	90	24
104	318	30	293	92	33	280	88	23

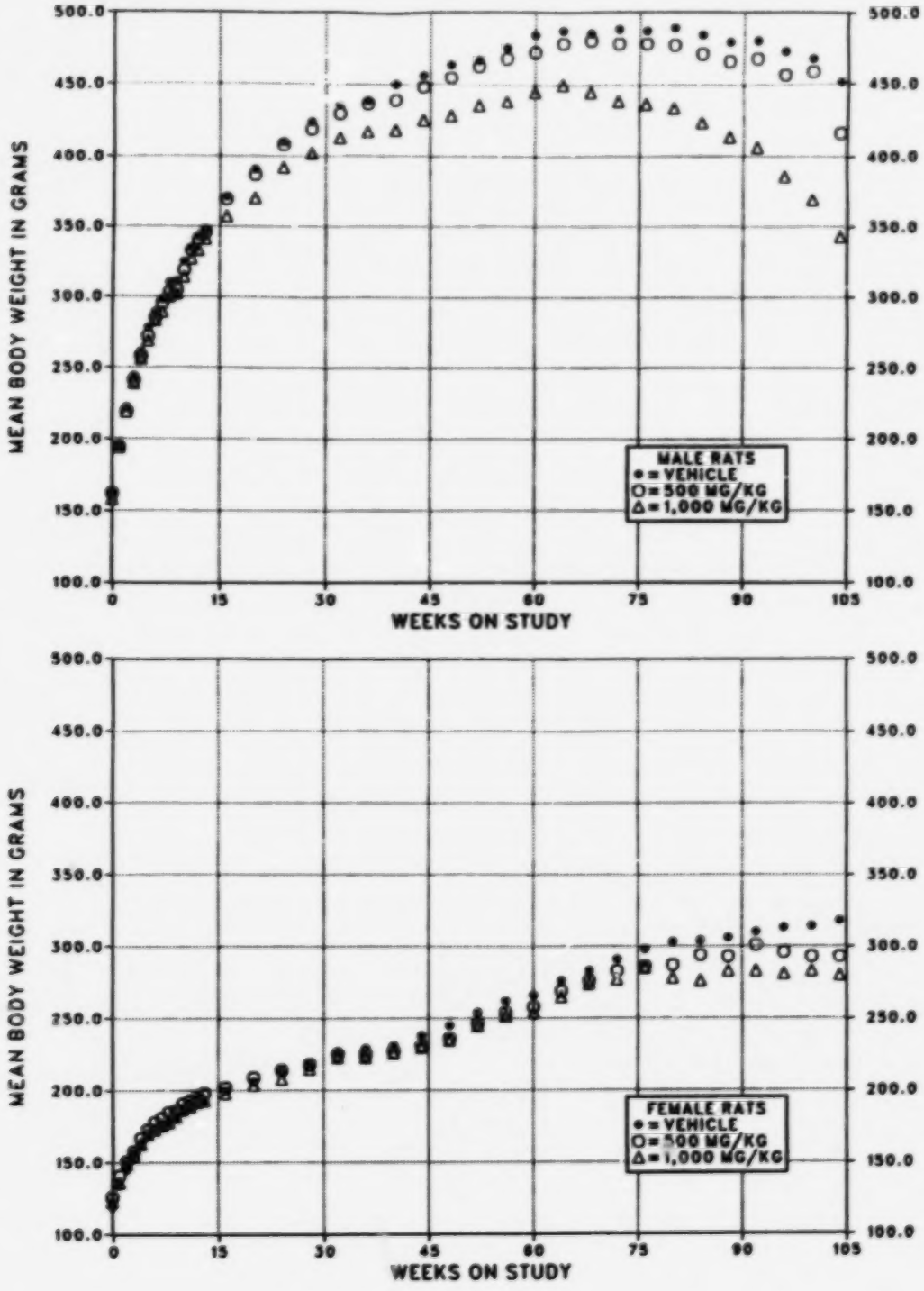

FIGURE 3. GROWTH CURVES FOR RATS ADMINISTERED DIMETHYL METHYLPHOSPHONATE IN CORN OIL BY GAVAGE FOR TWO YEARS

III. RESULTS: RATS

Survival

Estimates of the probabilities of survival for male and female rats administered dimethyl methylphosphonate at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 4. In male rats, the number of survivors in both the low dose group (after week 88) and the high dose group (after week 82) was significantly lower than that in the vehicle controls (Table 16). The survival of high dose female rats was significantly lower than that of the vehicle controls after week 63 ($P<0.05$; $P<0.01$ between weeks 76 and 101). Survival of low dose female rats was comparable to that of the vehicle controls.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the kidney, hematopoietic system, adrenal gland, oral cavity, thyroid gland, multiple organs, and nasolacrimal duct.

Lesions in male rats are summarized in Appendix A. Histopathologic findings on neoplasms are summarized in Table A1. Table A2 gives the survival and tumor status for individual male rats. Table A3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table A3 (footnotes). Historical incidences of tumors in corn oil vehicle control male rats are listed in Table A4. Findings on nonneoplastic lesions are summarized in Table A5.

Lesions in female rats are summarized in Appendix B. Histopathologic findings on neoplasms are summarized in Table B1. Table B2 gives the survival and tumor status for individual female rats. Table B3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table B3 (footnotes). Historical incidences of tumors in corn oil vehicle control female rats are listed in Table B4. Findings on nonneoplastic lesions are summarized in Table B5.

TABLE 16. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE

	Vehicle Control	500 mg/kg	1,000 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	22	33	45
Accidentally killed	1	0	1
Killed at termination	26	17	4
Died during termination period	1	0	0
Survival P values (c)	<0.001	0.031	<0.001
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	20	17	27
Killed at termination	30	32	23
Died during termination period	0	1	0
Survival P values (c)	0.044	0.720	0.049

(a) Terminal-kill period: week 105
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

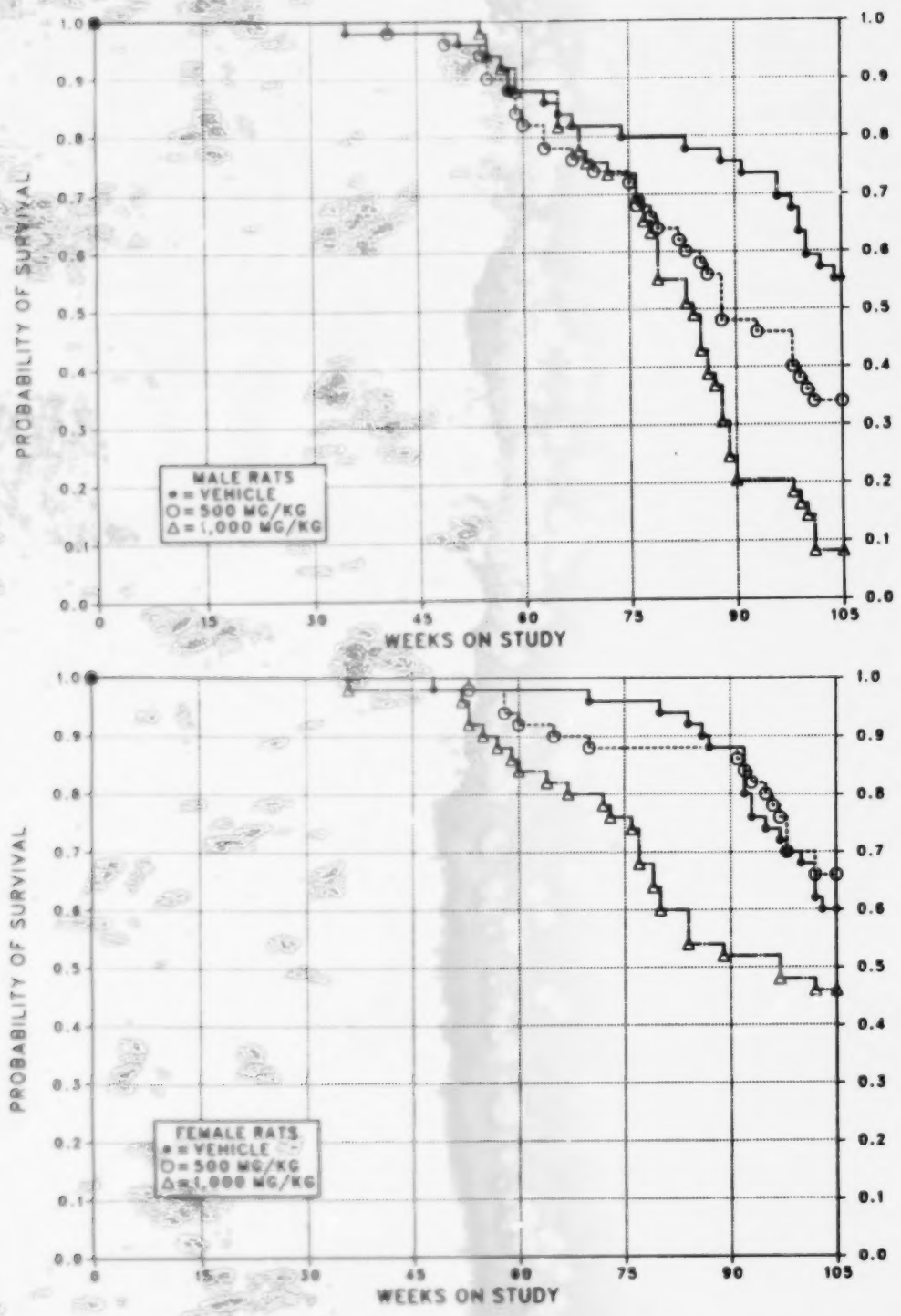

FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED DIMETHYL METHYLPHOSPHONATE IN CORN OIL BY GAVAGE FOR TWO YEARS

Kidney: Compound-related nonneoplastic and neoplastic lesions were seen in male but not in female rats (Table 17). The incidence of nephropathy was similar among groups of male rats, but the average severity of this lesion was greater in male rats receiving dimethyl methylphosphonate. The average severity for the vehicle control, low dose, and high dose groups was 1.9, 2.5, and 2.8, respectively (severity was graded from 1 to 4, minimal to marked). This lesion was characterized by the occurrence of several interrelated changes, including degeneration of tubular epithelium, tubular dilatation with attenuation and atrophy of the epithelium, granular casts in tubules of the outer stripe of the outer medulla, thickening of basement membranes, minimal to mild accumulation of interstitial collagen, and minimal inflammatory cell infiltrates. There were increased incidences of mineralization (calcification) of collecting tubules in the renal papilla, focal hyperplasia of renal tubular epithelium, and hyperplasia of the pelvic epithelium overlying the renal papilla of dosed male rats compared with those of the vehicle

TABLE 17. ANALYSIS OF KIDNEY LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (a)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Nephropathy			
Overall Rates	36/50 (72%)	43/50 (86%)	40/49 (82%)
Severity (b)	1.9	2.5	2.8
Calcification of the Renal Papilla			
Overall Rates	12/50 (24%)	41/50 (82%)	36/49 (73%)
Cortical Tubular Cell Hyperplasia			
Overall Rates	0/50 (0%)	8/50 (16%)	9/49 (18%)
Tubular Cell Adenocarcinoma (c)			
Overall Rates	0/50 (0%)	2/50 (4%)	3/49 (6%)
Adjusted Rates	0.0%	9.2%	19.4%
Terminal Rates	0/27 (0%)	1/17 (6%)	0/4 (0%)
Week of First Observation		88	77
Life Table Tests	P=0.014	P=0.160	P=0.043
Incidental Tumor Tests	P=0.091	P=0.288	P=0.167
Pelvic Epithelial Hyperplasia			
Overall Rates	0/50 (0%)	23/50 (46%)	21/49 (43%)
Transitional Cell Papilloma (d)			
Overall Rates	0/50 (0%)	7/50 (14%)	3/49 (6%)
Adjusted Rates	0.0%	38.5%	17.5%
Terminal Rates	0/27 (0%)	6/17 (35%)	0/4 (0%)
Week of First Observation		99	85
Life Table Tests	P=0.001	P<0.001	P=0.031
Incidental Tumor Tests	P=0.014	P=0.001	P=0.301
Transitional Cell Carcinoma			
Overall Rates	0/50 (0%)	1/50 (2%)	0/49 (0%)
Transitional Cell Papilloma or Carcinoma			
Overall Rates	0/50 (0%)	8/50 (16%)	3/49 (6%)
Adjusted Rates	0.0%	44.1%	17.5%
Terminal Rates	0/27 (0%)	7/17 (41%)	0/4 (0%)
Week of First Observation		99	85
Life Table Tests	P<0.001	P<0.001	P=0.031
Incidental Tumor Tests	P=0.010	P<0.001	P=0.301

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix A, Table A3 (footnotes).
(b) Severity of lesion graded from 1 to 4, minimal to marked
(c) Historical incidence of tubular cell adenomas or adenocarcinomas at study laboratory (mean): 3/450 (0.7%); historical incidence in NTP studies: 8/1,448 (0.6%)
(d) Historical incidence at study laboratory (mean): 0/450; historical incidence in NTP studies: 1/1,448 (<0.1%)

controls. The mineralization in vehicle control rats was minimal in severity and consisted of one or several small foci of mineral deposition. In dosed rats, there were many linear deposits of mineral, some extending almost the full depth of the papilla. Focal hyperplasia of the renal tubular epithelium consisted of single or multiple cross-sections of tubules filled or partialiy filled with stratified epithelial cells. The stratification of these cells and loss of basement membrane dependency differentiate this lesion from the epithelial regeneration occurring in response to the degenerative changes of spontaneous nephropathy. Hyperplasia of the renal pelvic epithelium was characterized by thickening and folding of the transitional epithelium to form small nodular structures protruding into the pelvic lumens.

Tubular cell adenocarcinomas in males occurred with a significant positive trend by the life table test, and the incidence in the high dose group was significantly greater than that in the vehicle controls by the life table test (Table 17). Transitional cell papillomas of the renal pelvis occurred in 7/50 low dose and 3/49 high dose rats; a transitional cell carcinoma occurred in a low dose male rat. Transitional cell papillomas and transitional cell papillomas or carcinomas (combined) in male rats occurred with significant positive trends; the incidences in the low dose group were greater than those in the vehicle controls.

Hematopoietic System: Mononuclear cell leukemia in male rats occurred with a significant positive trend; the incidence in the high dose group was significantly greater than that in the vehicle controls (Table 18); most of the leukemias were stage 3 and contributed to the deaths of the animals. Criteria for staging mononuclear cell leukemia are given below.

Stage 1. Spleen not enlarged or only slightly enlarged with small numbers of neoplastic mononuclear cells in the red pulp; no or very few mononuclear cells in the liver sinusoids. No identifiable neoplastic cells in other organs.

Stage 2. Spleen moderately enlarged with moderate to large numbers of mononuclear cells in the red pulp; architectural features including lymphoid follicles and periarteriolar lymphocytic sheaths remain intact. Minimal to moderate involvement of the liver. Mononuclear cells may be evident in blood vessels in other organs, but aggregates/masses of neoplastic cells generally limited to spleen and liver.

Stage 3. Advanced disease with multiple organ involvement. Spleen usually markedly enlarged with effacement of normal architectural features by accumulated neoplastic cells. Liver moderately to markedly enlarged and nodular; hepatic parenchyma shows variable degenerative changes associated with the accumulation of neoplastic cells. Accumulations of neoplastic mononuclear cells in other organs including lung, lymph nodes, kidney, brain, and adrenal gland.

TABLE 18. ANALYSIS OF MONONUCLEAR CELL LEUKEMIA IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (a)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Overall Rates	10/50 (20%)	11/50 (22%)	17/50 (34%)
Adjusted Rates	30.0%	38.5%	100.0%
Terminal Rates	4/27 (15%)	4/17 (24%)	4/4 (100%)
Week of First Observation	91	63	76
Life Table Tests	P<0.001	P=0.188	P<0.001
Incidental Tumor Tests	P=0.048	P=0.493	P=0.032
Stage			
1	0	3	0
2	4	2	4
3	6	6	13
Average stage leukemia	2.60	2.27	2.76

(a) Historical incidence of leukemia at study laboratory (mean ± SD): 85/450 (19% ± 9%); historical incidence in NTP studies: 202/1,450 (14% ± 8%)

Oral Cavity (mouth, palate, or tongue): Squamous cell papillomas or carcinomas (combined) in female rats occurred with a marginally significant positive trend by the life table test (vehicle control, 1/50; low dose, 0/50; high dose, 4/50; P=0.045). The incidence in the high dose group was not significantly greater than that in the vehicle controls.

Adrenal Gland: Pheochromocytomas and pheochromocytomas or malignant pheochromocytomas (combined) in male rats occurred with significant positive trends (Table 19).

TABLE 19. ANALYSIS OF ADRENAL GLAND LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE

	Vehicle Control	500 mg/kg	1,000 mg/kg
Medullary Focal Hyperplasia			
Overall Rates	12/50 (24%)	8/50 (16%)	10/49 (20%)
Pheochromocytoma			
Overall Rates	12/50 (24%)	14/50 (28%)	18/49 (37%)
Adjusted Rates	35.5%	57.8%	91.3%
Terminal Rates	7/27 (26%)	8/17 (47%)	3/4 (75%)
Week of First Observation	55	70	65
Life Table Tests	P<0.001	P=0.092	P<0.001
Incidental Tumor Tests	P=0.022	P=0.284	P=0.071
Malignant Pheochromocytoma			
Overall Rates	0/50 (0%)	4/50 (8%)	0/49 (0%)
Adjusted Rates	0.0%	18.5%	0.0%
Terminal Rates	0/27 (0%)	2/17 (12%)	0/4 (0%)
Week of First Observation		86	
Life Table Tests	P=0.236	P=0.026	(a)
Incidental Tumor Tests	P=0.486	P=0.052	(a)
Pheochromocytoma or Malignant Pheochromocytoma (b)			
Overall Rates	12/50 (24%)	18/50 (36%)	18/49 (37%)
Adjusted Rates	35.5%	69.7%	91.3%
Terminal Rates	7/27 (26%)	10/17 (59%)	3/4 (75%)
Week of First Observation	55	70	65
Life Table Tests	P<0.001	P=0.012	P<0.001
Incidental Tumor Tests	P=0.017	P=0.069	P=0.071

(a) No P value is reported because no tumors were observed in the 1,000 mg/kg and vehicle control groups.
(b) Historical incidence of pheochromocytomas or malignant pheochromocytomas at study laboratory (mean ± SD): 98/449 (22% ± 9%); historical incidence in NTP studies: 347/1,442 (24% ± 9%)

Thyroid Gland: C-Cell carcinomas, considered a nonfatal tumor, occurred in male rats with a significant positive trend; the incidence in the high dose group was significantly greater than that in the vehicle controls, but the incidences of C-cell adenomas or carcinomas (combined) in dosed male rats were not significantly different from that in the vehicle controls by the incidental tumor test (Table 20). The incidences of follicular cell adenomas or carcinomas (combined) in dosed male rats were increased by the life table trend test but only marginally by the incidental tumor trend test, the latter being the more appropriate test for nonfatal tumors (Table 21). The incidences of thyroid gland tumors were not increased in female rats.

TABLE 20. ANALYSIS OF THYROID GLAND C-CELL LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE

	Vehicle Control	500 mg/kg	1,000 mg/kg
Hyperplasia			
Overall Rates	6/49 (12%)	6/50 (12%)	3/49 (6%)
Adenoma			
Overall Rates	3/49 (6%)	0/50 (0%)	1/49 (2%)
Carcinoma			
Overall Rates	1/49 (2%)	4/50 (8%)	4/49 (8%)
Adjusted Rates	3.7%	20.6%	54.3%
Terminal Rates	1/27 (4%)	3/17 (18%)	2/4 (50%)
Week of First Observation	105	88	79
Life Table Tests	P=0.002	P=0.075	P=0.004
Incidental Tumor Tests	P=0.022	P=0.122	P=0.030
Adenoma or Carcinoma (a)			
Overall Rates	4/49 (8%)	4/50 (8%)	5/49 (10%)
Adjusted Rates	14.8%	20.6%	57.3%
Terminal Rates	4/27 (15%)	3/17 (18%)	2/4 (50%)
Week of First Observation	105	88	79
Life Table Tests	P=0.008	P=0.387	P=0.008
Incidental Tumor Tests	P=0.112	P=0.486	P=0.118

(a) Historical incidence at study laboratory (mean ± SD): 39/437 (9% ± 3%); historical incidence in NTP studies: 181/1,417 (13% ± 6%)

TABLE 21. ANALYSIS OF THYROID GLAND FOLLICULAR CELL LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE

	Vehicle Control	500 mg/kg	1,000 mg/kg
Hyperplasia			
Overall Rates	0/49 (0%)	1/50 (2%)	0/49 (0%)
Adenoma			
Overall Rates	0/49 (0%)	0/50 (0%)	2/49 (4%)
Carcinoma			
Overall Rates	0/49 (0%)	2/50 (4%)	1/49 (2%)
Adenoma or Carcinoma (a)			
Overall Rates	0/49 (0%)	2/50 (4%)	3/49 (6%)
Adjusted Rates	0.0%	11.8%	22.9%
Terminal Rates	0/27 (0%)	2/17 (12%)	0/4 (0%)
Week of First Observation		105	88
Life Table Tests	P=0.003	P=0.143	P=0.014
Incidental Tumor Tests	P=0.050	P=0.143	P=0.301

(a) Historical incidence at study laboratory (mean ± SD): 6/437 (1% ± 2%); historical incidence in NTP studies: 35/1,417 (2% ± 3%)

Multiple Organs: Mesotheliomas in the tunica vaginalis in male rats occurred with a significant positive trend; however, the incidence of total mesotheliomas at all sites was only marginally increased when analyzed by the incidental tumor trend test, and the incidence of mesotheliomas (all sites) in dosed animals was not greater than the vehicle control incidence in pairwise comparisons with the vehicle controls by the life table test (Table 22).

Nasolacrimal Duct: Chronic inflammation was observed at an increased incidence in high dose male rats (male: vehicle control, 1/50; low dose, 1/50; high dose, 8/50); this lesion was not notably increased in dosed females (0/50; 0/50; 2/50).

TABLE 22. ANALYSIS OF MESOTHELIOMAS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE

	Vehicle Control	500 mg/kg	1,000 mg/kg
Tunica Vaginalis			
Overall Rates	0/50 (0%)	4/50 (8%)	6/50 (12%)
Adjusted Rates	0.0%	20.2%	34.3%
Terminal Rates	0/27 (0%)	3/17 (18%)	0/4 (0%)
Week of First Observation		82	68
Life Table Tests	P<0.001	P=0.025	P=0.002
Incidental Tumor Tests	P=0.007	P=0.044	P=0.046
All Sites (a)			
Overall Rates	(b) 2/50 (4%)	5/50 (10%)	6/50 (12%)
Adjusted Rates	6.4%	25.9%	34.3%
Terminal Rates	1/27 (4%)	4/17 (24%)	0/4 (0%)
Week of First Observation	96	82	68
Life Table Tests	P=0.002	P=0.083	P=0.009
Incidental Tumor Tests	P=0.034	P=0.130	P=0.141

(a) Historical incidence of mesotheliomas at all sites at study laboratory (mean ± SD): 20/450 (4% ± 3%); historical incidence in NTP studies: 55/1,450 (4% ± 3%)
(b) Includes one malignant mesothelioma

SINGLE-ADMINISTRATION STUDIES

Two of five female mice in the highest (6,810 mg/kg) dose group died before the end of the studies; all other mice survived to the end of the studies. No gross pathologic effects were observed in the two female mice that died. Transitory inactivity (1-4 hours after dosing) was observed in the two highest dose groups. Higher doses (0, 1,250, 2,500, 5,000, 10,000, and 15,000 mg/kg) were selected for the 15-day studies because the oral LD_{50} value was judged to be greater than 6,810 mg/kg.

FIFTEEN-DAY STUDIES

All the mice that received 15,000 mg/kg and 4/5 males and 5/5 females that received 10,000 mg/kg died before the end of the studies (Table 23). Inactivity, prostration, and shallow breathing were seen in animals dying after dosing in the 10,000 and 15,000 mg/kg groups. Various stomach lesions were observed at increased incidences in the three highest dose groups of females (gastropathy, gastritis, hyperkeratosis, or epithelial ulceration) and in all dosed groups of males (squamous atrophy, gastropathy, or gastritis) (Table 24). Based on the mortality at the 10,000 and 15,000 mg/kg doses, a high dose of 8,000 mg/kg was selected for the 13-week studies.

TABLE 23. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FIFTEEN-DAY GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	28	27	−1	--
1,250	(c) 4/5	28	28	0	103.7
2,500	5/5	28	26	−2	96.3
5,000	5/5	27	28	+1	103.7
10,000	(d) 1/5	27	22	−5	81.5
15,000	(e) 0/5	27	(f)	(f)	(f)
FEMALE					
0	5/5	20	20	0	--
1,250	5/5	20	20	0	100.0
2,500	5/5	20	19	−1	95.0
5,000	5/5	20	20	0	100.0
10,000	(g) 0/5	20	(f)	(f)	(f)
15,000	(h) 0/5	20	(f)	(f)	(f)

(a) Number surviving/number initially in group
(b) Initial group mean body weight
(c) Day of death: 8, death judged not compound related
(d) Day of death: 2,7,8,15
(e) Day of death: 2,2,2,2,3
(f) No data are reported due to the 100% mortality in this group.
(g) Day of death: 2,7,10,11,15
(h) Day of death: all 1

TABLE 24. NUMBERS OF MICE WITH STOMACH LESIONS IN THE FIFTEEN-DAY GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE

Lesion	Dose (mg/kg)					
	0	1,250	2,500	5,000	10,000	15,000
MALE						
No. of animals examined	5	5	5	5	5	5
Insufficient tissue for evaluation	0	0	1	0	1	0
Autolysis	0	0	0	0	1	0
Epithelial necrosis	0	0	1	0	1	0
Submucosal necrosis	0	0	0	0	1	0
Squamous atrophy	0	0	0	0	1	3
Hyperplastic gastropathy	0	1	0	1	0	1
Hyperplastic gastritis, acute/chronic	0	0	1	0	2	0
Hyperkeratosis	0	0	0	0	0	0
Epithelial ulceration	0	0	0	0	0	0
FEMALE						
No. of animals examined	5	5	5	5	5	5
Autolysis	0	0	0	0	0	0
Epithelial necrosis	0	0	0	0	0	0
Submucosal necrosis	0	0	0	0	0	0
Squamous atrophy	0	0	0	0	0	0
Hyperplastic gastropathy	0	0	0	2	0	1
Hyperplastic gastritis, acute/chronic	0	0	0	1	3	0
Hyperkeratosis	0	0	0	0	0	2
Epithelial ulceration	0	0	0	0	3	0

THIRTEEN-WEEK STUDIES

Seven of seven males and 5/6 females that received 8,000 mg/kg and 9/10 males and 9/10 females that received 4,000 mg/kg dimethyl methylphosphonate died before the end of the studies (Table 25). The final mean body weights of the dosed and vehicle control groups were comparable. No compound-related clinical signs or gross or microscopic lesions were observed.

Dose Selection Rationale: Based on the incidences of deaths and body weight effects, doses selected for mice for the 2-year studies were 1,000 and 2,000 mg/kg dimethyl methylphosphonate, administered in corn oil by gavage, 5 days per week for 103 weeks.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male mice were 7%-16% lower than those of vehicle controls between weeks 36 and 76 (Table 26, and Figure 5). Mean body weights of high dose female mice were 6%-12% lower than those of the vehicle controls between week 88 and week 103. No compound-related clinical signs were reported.

TABLE 25. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	23	29	+6	--
250	10/10	23	30	+7	103.4
500	10/10	24	32	+8	110.3
1,000	10/10	24	32	+8	110.3
2,000	10/10	24	32	+8	110.3
4,000	(d) 1/10	25	28	+3	96.6
8,000	(e) 0/7	(f)	(g)	--	(g)
FEMALE					
0	10/10	19	24	+5	--
250	10/10	19	24	+5	100.0
500	10/10	18	24	+6	100.0
1,000	10/10	19	24	+5	100.0
2,000	10/10	19	24	+5	100.0
4,000	(h) 1/10	19	23	+4	95.8
8,000	(i) 1/6	(f)	25	--	104.2

(a) Number surviving/number initially in group
(b) Initial group mean body weight
(c) Mean body weight change of the survivors
(d) Week of death: 2,5,6,6,6,6,6,9,9
(e) Week of death: 1,3,3,3,3,3,4
(f) Initial weights not reported
(g) No data are reported due to the 100% mortality in this group.
(h) Week of death: 8,9,9,10,10,12,12,12,12
(i) Week of death: 2,6,6,10,11

TABLE 26. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	1,000 mg/kg Av. Wt. (grams)	1,000 mg/kg Wt. (percent of veh. controls)	1,000 mg/kg No. of Survivors	2,000 mg/kg Av. Wt. (grams)	2,000 mg/kg Wt. (percent of veh. controls)	2,000 mg/kg No. of Survivors
MALE								
0	22.4	50	23.0	103	50	22.0	98	50
1	21.9	49	23.8	109	50	23.1	105	50
2	24.6	49	25.0	102	49	24.4	99	50
3	26.4	49	26.1	99	49	25.3	96	50
4	26.8	49	27.0	101	49	26.1	97	49
5	27.4	49	27.4	100	49	26.2	96	49
6	28.4	49	28.7	101	49	27.7	98	49
7	28.6	49	29.2	102	49	28.5	100	49
8	29.4	49	29.3	100	49	28.9	98	49
9	30.3	49	30.7	101	49	30.1	99	49
10	30.8	49	30.9	100	49	30.4	99	49
11	31.1	48	30.9	99	49	30.6	98	48
12	31.3	48	31.2	100	49	30.5	97	48
13	31.3	48	31.6	101	49	30.9	99	48
16	32.4	47	32.7	101	49	31.7	98	48
20	34.3	47	33.8	99	48	33.1	97	44
24	35.0	47	34.7	99	45	33.3	95	39
28	36.4	45	35.9	99	45	34.8	96	37
32	37.5	44	37.2	99	45	35.8	95	36
36	38.9	44	38.2	98	45	36.1	93	33
40	38.7	44	38.7	100	44	35.9	93	32
44	41.3	43	40.7	99	44	37.4	91	28
48	41.4	41	41.2	100	44	36.3	88	11
52	41.9	41	42.5	101	44	37.1	89	11
56	42.8	41	43.5	102	42	38.3	89	11
60	44.8	40	44.4	99	42	37.5	84	11
64	42.4	40	43.6	103	41	38.8	92	11
68	44.1	40	43.1	98	41	39.1	89	10
72	44.1	40	43.5	99	41	39.5	90	8
76	45.0	40	43.1	96	40	39.5	88	6
80	44.8	38	43.7	98	29	42.8	96	4
84	44.3	38	43.4	98	27	45.3	102	3
88	44.1	36	42.3	96	26	45.0	102	3
92	43.0	35	43.0	100	25	45.3	105	3
96	41.3	32	41.1	100	19	--	--	--
100	40.6	31	42.3	104	13	--	--	--
104	39.4	30	39.8	101	12	--	--	--
FEMALE								
0	17.6	50	18.3	104	50	18.0	102	50
1	18.1	50	19.1	106	50	18.5	102	50
2	18.9	50	19.7	104	50	19.2	102	50
3	20.0	50	20.2	101	50	19.8	99	50
4	20.0	50	20.4	102	50	20.0	100	50
5	20.2	50	20.5	101	50	20.3	100	50
6	21.1	50	21.2	100	50	21.1	100	50
7	21.1	50	21.7	103	50	21.4	101	50
8	21.6	50	22.1	102	50	21.4	99	50
9	21.9	50	22.8	104	50	22.3	102	50
10	22.2	50	22.6	103	50	22.7	102	50
11	22.5	50	23.0	102	50	22.8	101	50
12	22.4	50	22.9	102	50	22.5	100	50
13	22.5	50	23.3	104	50	22.9	102	50
16	23.5	50	23.7	101	50	23.4	100	50
20	24.5	50	25.0	102	49	24.3	99	47
24	24.7	50	25.3	102	49	24.6	100	47
28	25.6	50	26.0	102	49	25.9	101	47
32	27.2	50	27.6	101	49	26.9	99	46
36	28.3	50	28.7	101	47	27.9	99	45
40	28.4	50	29.1	102	47	28.1	99	45
44	30.6	48	30.8	101	47	29.7	97	43
48	30.7	48	31.4	102	47	30.4	99	21
52	31.5	48	32.4	103	47	31.0	98	21
56	33.4	48	34.0	102	47	32.4	97	20
60	35.0	48	35.3	101	47	33.1	95	19
64	34.2	47	35.8	105	48	34.0	99	19
68	35.2	47	36.6	104	45	35.5	101	18
72	36.5	47	37.1	102	45	35.1	96	10
76	37.4	47	38.4	103	44	36.1	97	8
80	38.0	47	38.9	102	44	37.4	98	7
84	38.6	47	39.9	103	44	36.5	95	6
88	38.3	47	39.6	103	44	36.0	94	4
92	38.9	46	40.4	104	44	34.3	88	3
96	38.3	45	39.8	103	38	34.3	90	3
100	38.1	44	40.0	105	35	35.3	93	3
104	37.3	42	39.0	105	31	36.5	98	2

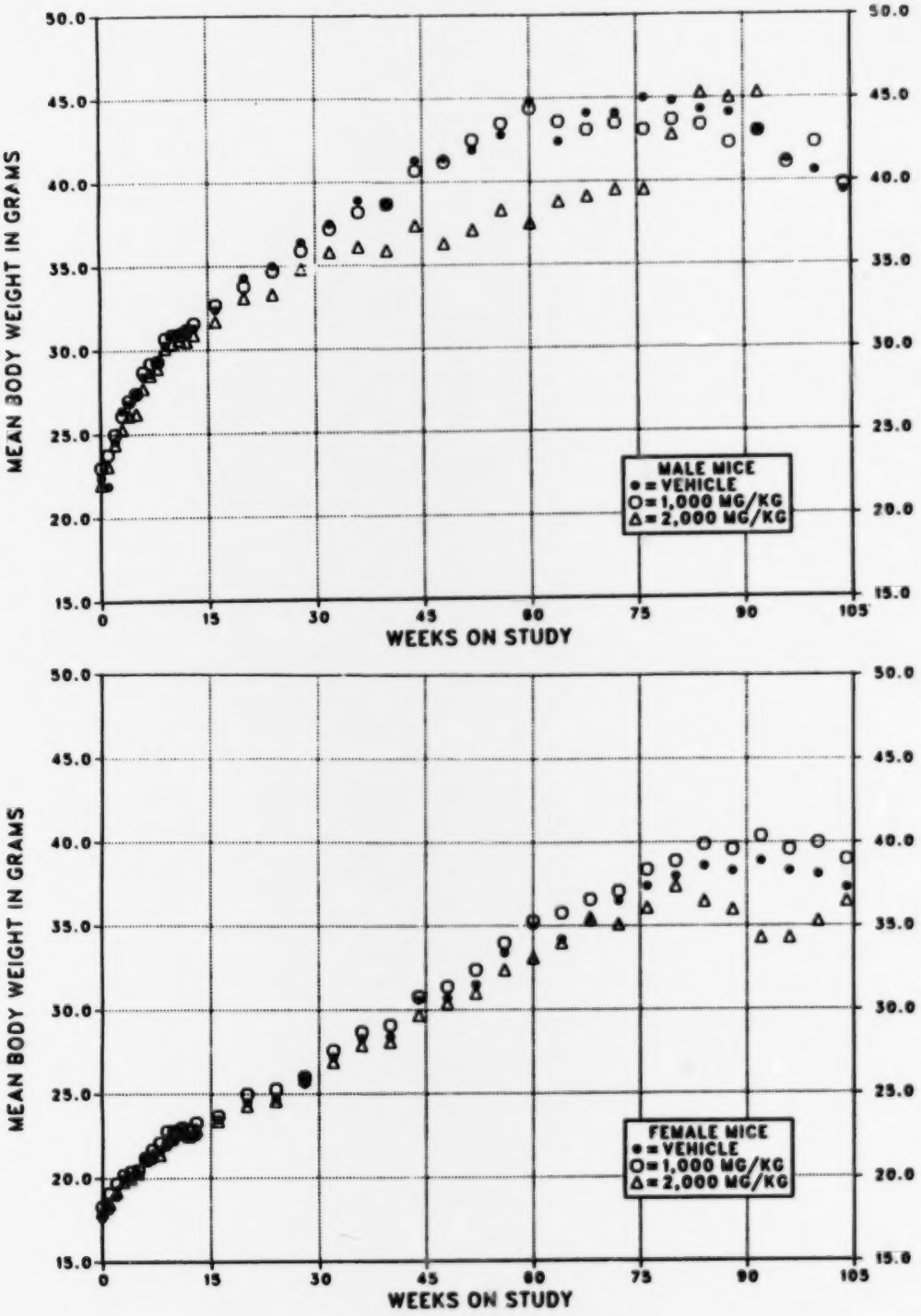

FIGURE 5. GROWTH CURVES FOR MICE ADMINISTERED DIMETHYL METHYLPHOSPHONATE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered dimethyl methylphosphonate at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 6. Between weeks 23 and 44, there was a gradual decrease in survival in high dose male mice which was attributed to fighting; lesions around the penis were noted in many of these animals. Aggressive animals were housed separately to prevent animal attrition. At week 45, 17 high dose male mice and 22 high dose female mice were found dead; chemical analysis of the dose preparation found the dose to be 134% of the targeted amount. For purposes of survival analysis, these deaths were censored. Eleven low dose male mice died at week 77.

The survival of both the low dose (after week 95) and the high dose (after week 23) groups of male mice was significantly lower than that of the vehicle controls (Table 27). The survival of the high dose group of female mice was significantly lower than that of the vehicle controls after week 52. The survival of the low dose female mice was comparable to that of the vehicle controls. Unadjusted survival curves (with accidental deaths not censored) for male and female mice are shown in Figure 7.

TABLE 27. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYL METHYLPHOSPHONATE

	Vehicle Control	1,000 mg/kg	2,000 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	17	33	33
Accidentally killed	4	5	17
Killed at termination	28	12	0
Died during termination period	1	0	0
Survival P values (c)	<0.001	0.004	<0.001
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	7	14	24
Accidentally killed	0	6	23
Animals missing	2	0	1
Killed at termination	41	30	2
Survival P values (c)	<0.001	0.109	<0.001

(a) Terminal-kill period: week 105
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

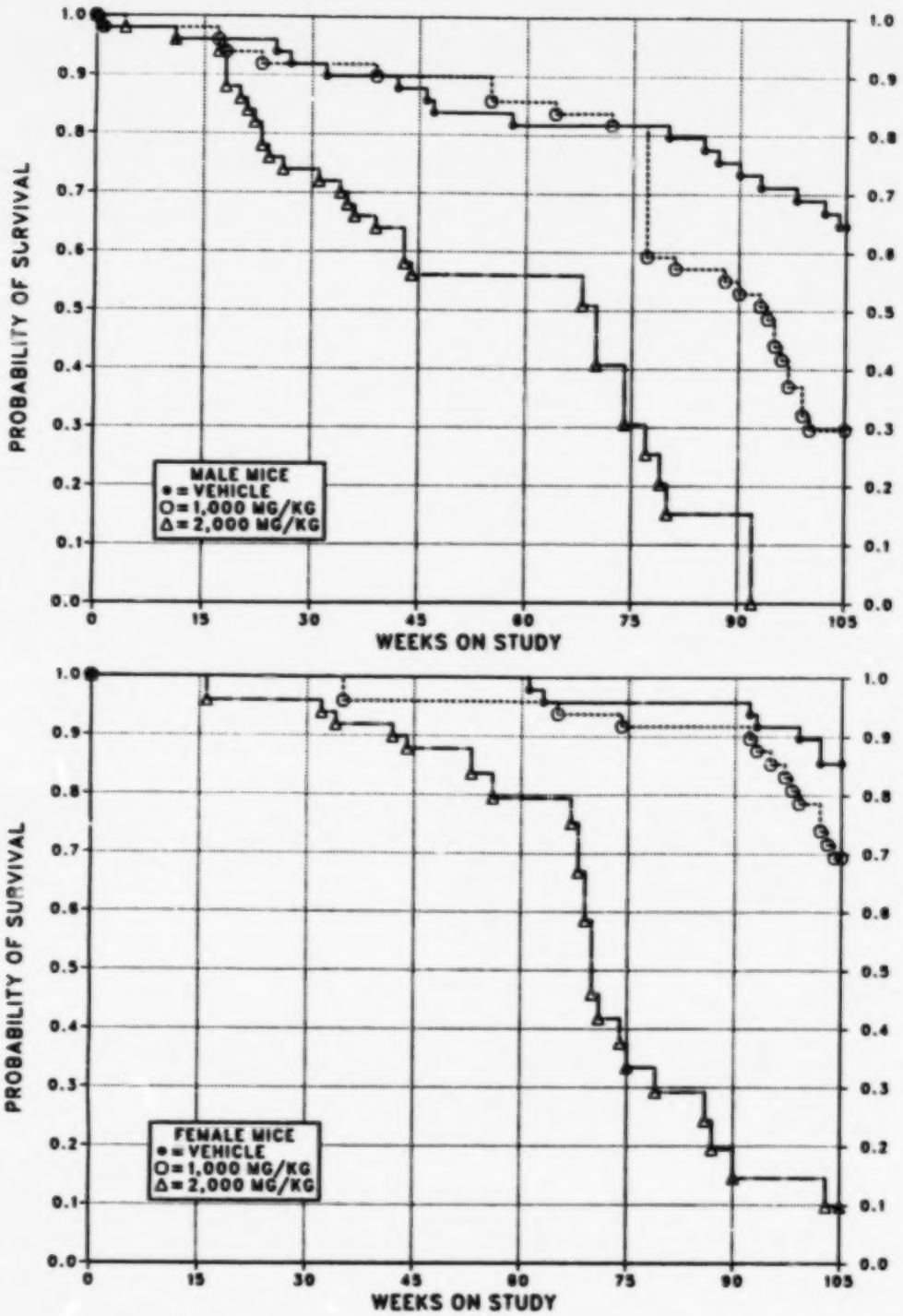

FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED DIMETHYL METHYLPHOSPHONATE IN CORN OIL BY GAVAGE FOR TWO YEARS

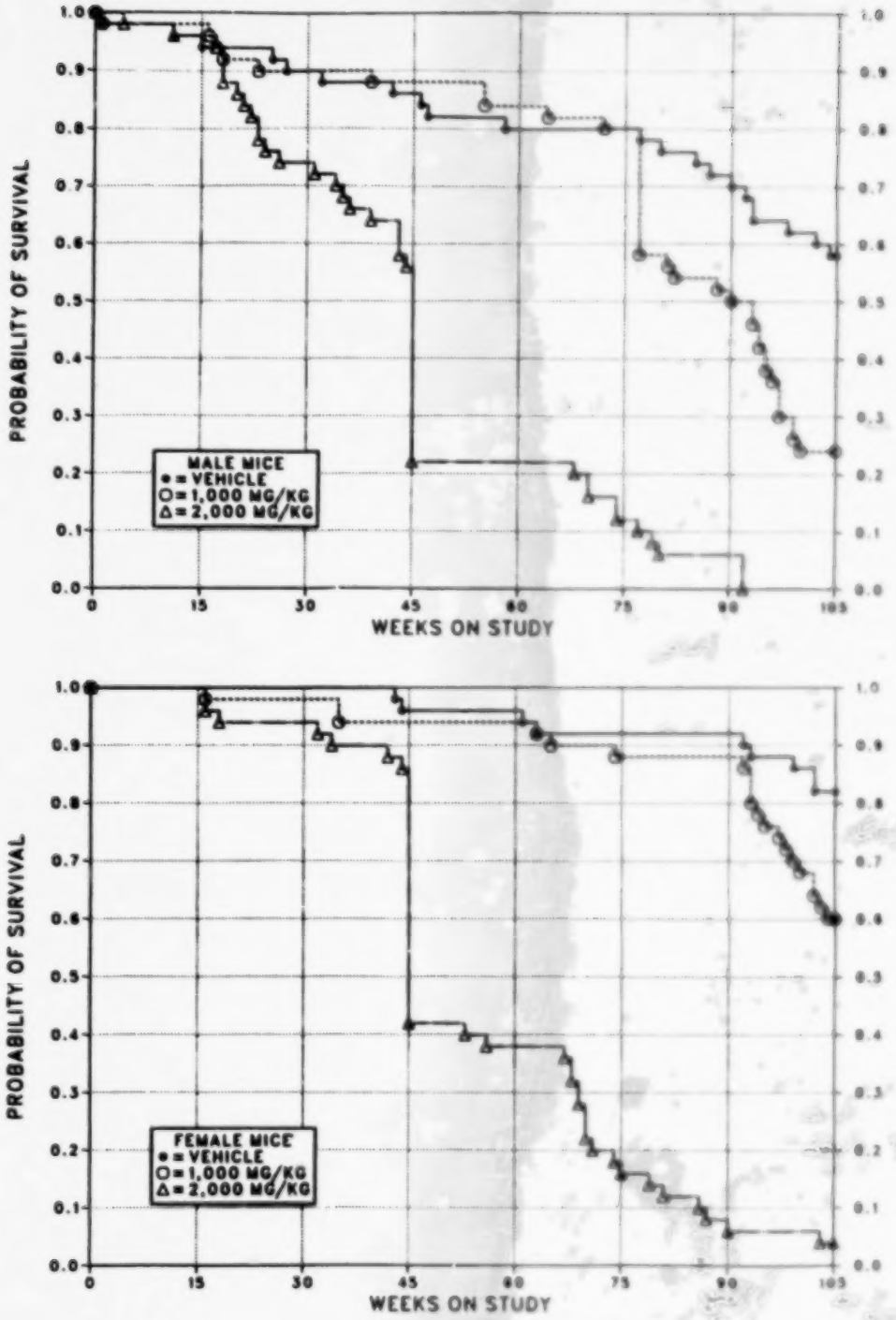

FIGURE 7. UNADJUSTED SURVIVAL CURVES FOR MICE ADMINISTERED DIMETHYL METHYLPHOSPHONATE IN CORN OIL BY GAVAGE FOR TWO YEARS

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the liver, hematopoietic system, and lung.

Lesions in male mice are summarized in Appendix C. Histopathologic findings on neoplasms are summarized in Table C1. Table C2 gives the survival and tumor status for individual male mice. Table C3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table C3 (footnotes). Historical incidences of tumors in corn oil vehicle control male mice are listed in Table C4. Findings on nonneoplastic lesions are summarized in Table C5.

Lesions in female mice are summarized in Appendix D. Histopathologic findings on neoplasms are summarized in Table D1. Table D2 gives the survival and tumor status for individual female mice. Table D3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table D3 (footnotes). Findings on nonneoplastic lesions are summarized in Table D4. The increased mortality in the high dose groups resulted in little overlap of survival times; thus, the sensitivity of the incidental tumor test for detecting carcinogenic effects was reduced.

Liver: Hepatocellular adenomas and hepatocellular adenomas or carcinomas (combined) in male mice occurred with significant positive trends by the life table test ($P<0.001$) but not by the incidental tumor test ($P=0.156$), the more appropriate test for nonfatal tumors such as these (vehicle control, 17/50; low dose, 21/50; high dose, 4/46). Hepatocytomegaly was observed at increased incidences in dosed male mice (5/50; 17/50; 10/46). No increase in neoplastic or nonneoplastic liver lesions was seen in dosed female mice.

Hematopoietic System: Malignant lymphomas in male mice occurred with a significant positive trend by the life table test (vehicle control, 2/50; low dose, 3/50; high dose, 1/50; $P=0.026$). One vehicle control male mouse had granulocytic leukemia. Because final survival in high dose animals was lower than that in the other groups, there were fewer high dose animals at risk for leukemia. Female mice showed no significant increases in the incidence of either malignant lymphomas or leukemia.

Lung: Congestion was observed at increased incidences in dosed male mice (vehicle control, 2/50; low dose, 8/49; high dose, 16/45) and dosed female mice (0/48; 2/50; 14/49). The lung congestion was associated with early death, dosing errors, or gavage accidents. All animals (with the exception of one low dose female) with lung congestion died early in the studies; 14/16 high dose male mice and 11/14 high dose female mice with lung congestion died at week 45 when a dosing error was observed. Six of eight low dose male mice with lung congestion died at week 77, the week of an unexplained clustering of deaths.

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IV. DISCUSSION AND CONCLUSIONS

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Two-Year Studies in Mice
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IV. DISCUSSION AND CONCLUSIONS

Study Design

Dimethyl methylphosphonate was nominated for study in 1976 by the U.S. Army because it was a candidate nerve gas simulant. Three other candidate simulants were nominated for study at the same time, and it was recommended that all chemicals be studied in the same way so that toxicity data could be compared. In the short-term and 2-year studies, the chemicals were administered by gavage in corn oil to F344/N rats and B6C3F$_1$ mice to mimic potential oral exposure. Water was used as the vehicle in the studies of reproductive effects in male rodents.

Short-Term Studies

In the single-administration studies, dimethyl methylphosphonate was given to rats and mice at doses up to 6,810 mg/kg. No compound-related deaths were seen in rats or in male mice; two high dose female mice died. In the 15-day studies, rats and mice received doses up to 15,000 mg/kg per day. Compound-related deaths occurred at 5,000, 10,000, and 15,000 mg/kg in rats and at 10,000 and 15,000 mg/kg in mice. No compound-related lesions were seen in rats in these studies, but stomach lesions were seen in mice at 5,000, 10,000, and 15,000 mg/kg in the 15-day studies.

In the 13-week studies, dimethyl methylphosphonate was given at doses up to 8,000 mg/kg. Compound-related deaths occurred at 2,000, 4,000, and 8,000 mg/kg in rats and at 4,000 and 8,000 mg/kg in mice. During the single-administration and 15-day studies, clinical signs reported in rats and mice after dosing included inactivity, unsteady gait, and prostration; these clinical signs were not observed in the 13-week studies. No weight effects were observed in rats at 1,000 mg/kg or in mice at 2,000 mg/kg; reduced body weights and deaths were seen at higher doses. Minimal to mild renal and testicular lesions were seen in dosed male rats; no target tissues were identified in female rats or male and female mice. Doses selected for the 2-year studies were based on body weight effects and deaths observed in the short-term studies. The severity of the kidney lesions, which were observed in male rats at all doses, did not increase with increasing dose of the chemical. These lesions were not considered to be life threatening.

Like the kidney lesions, the testicular lesions in male rats were seen at all doses, and the severity was not increased as the dose increased. The reproductive effects of the chemical in male rats and mice were studied to further assess the effects of the chemical. In these studies, male F344/N rats and B6C3F$_1$ mice were administered dimethyl methylphosphonate by gavage in water at doses up to 2,000 mg/kg for 13 weeks and were mated to undosed females; necropsies were performed, and the testis, kidney, and sperm were examined. An increase in the number of fetal resorptions was seen when dosed male rats and mice were mated to undosed females. Lesions of the kidney and testis were seen in male rats but not in male mice, and decreased sperm count and motility were seen in male rats but not in male mice. Toxic effects to the reproductive system were seen in both male rats and mice. These effects were more severe in rats but were reversible after a 13- to 14-week recovery period without dosing. No clinical signs were observed after dosing (Dunnick et al., 1984a,b; Chapin et al., 1984).

Two-Year Studies in Rats

In the 2-year studies, dimethyl methylphosphonate was administered to rats at doses of 0, 500, or 1,000 mg/kg. Survival of dosed male rats was greater than 50% in all groups until week 80 but was reduced in both dosed groups in the last weeks of the study (final survival: vehicle control, 27/50; low dose, 17/50; high dose, 4/50). This decreased survival in dosed male rats was due in part to chemically related kidney toxicity. Final survival in high dose female rats was reduced (30/50; 33/50; 23/50). Mean body weights of high dose male rats were 5%-10% lower than those of the vehicle controls between weeks 28 and 76 and were 10%-24% lower between weeks 80 and 104. Mean body weights of high dose female rats were 8%-12% lower than those of the vehicle controls after week 80. No compound-related clinical signs were observed.

Dimethyl methylphosphonate administration was associated with increased severity of

nephropathy and increased incidence of mineralization (calcification) in the kidney of dosed male rats. Renal tubular cell adenocarcinomas (vehicle control, 0/50; low dose, 2/50; high dose, 3/49) and transitional cell papillomas or carcinomas (combined) of the pelvic epithelium (0/50; 8/50; 3/49) were seen in the kidney of dosed male rats. These are uncommon tumors in F344/N rats and are believed to be related to the administration of dimethyl methylphosphonate. This is supported by the incidences of tubular cell hyperplasia in dosed male rats. The incidence of tubular cell hyperplasia is often increased in association with the induction of tubular cell neoplasms, and there appears to be a morphologic spectrum suggesting progression from hyperplasia to adenoma to adenocarcinoma. Similarly, there is a morphologic spectrum from hyperplasia of the transitional epithelium to papilloma and carcinoma of the renal pelvis. The reduced survival of the high dose male rats may account for the smaller number of these neoplasms in this group.

The spectrum of renal toxicity in male rats given dimethyl methylphosphonate by gavage for 13 weeks and 2 years is similar to that in male rats exposed to gasoline vapors, related petroleum naphthas, or light hydrocarbons consisting of paraffins or cycloparaffins or to alkyl aromatic hydrocarbons, decalin (Mehlman et al., 1984), or 1,4-dichlorobenzene (NTP, 1987). Degeneration and regeneration of epithelium in proximal convoluted tubules and dilated tubules filled with granular proteinaceous material were observed in male rats exposed to light hydrocarbon compounds in short-term inhalation studies (Mehlman et al., 1984); similar lesions were seen in the short-term studies of 1,4-dichlorobenzene (NTP, 1987) and dimethyl methylphosphonate. Early lesions consisting of the accumulation of hyaline droplets in epithelial cells in the kidney of male rats have been demonstrated to be phagolysosomes filled with amorphous electron-dense material. Hyaline droplets formed within renal tubular cells of male rats after exposure to hydrocarbons were reported to be primarily α-2-microglobulin, a protein that is produced in the liver of male rats under the influence of testosterone (Phillips and Cockrell, 1984). Whether this protein plays a role in the pathogenesis of lesions associated with long-term administration of dimethyl methylphosphonate in male rats is unknown.

In contrast to the kidney lesions seen in male rats after exposure to dimethyl methylphosphonate, the major nonneoplastic lesions seen in the kidney of both rats and mice after exposure to halogenated hydrocarbons such as trichloroethylene (NTP, unpublished), 2-chloroethanol (NTP, 1985b), and tetrachloroethylene (NTP, 1986b) are cytomegaly, karyomegaly, and toxic nephrosis.

The incidence of mononuclear cell leukemia was increased in high dose male rats (vehicle control, 10/50; low dose, 11/50; high dose, 17/50), and the incidence exceeded the highest incidence seen in historical vehicle control groups in the NTP studies. Staging of the leukemia indicated that most of the tumors were stage 3.

Dosed male rats had marginally increased incidences of pheochromocytomas of the adrenal gland (vehicle control, 12/50; low dose, 14/50; high dose, 18/49). Four malignant pheochromocytomas also were seen in low dose male rats. The incidences in the dosed male rats slightly exceeded the highest incidence recorded for historical vehicle controls at the study laboratory (Appendix A, Table A4c), but the results of pairwise comparisons of low and high dose incidence to vehicle control incidence were not significant by the incidental tumor test, the test more appropriate for analysis of this nonfatal tumor.

Squamous cell papillomas or carcinomas (combined) of the oral cavity (mouth, palate, or tongue) in female rats occurred with a marginally significant ($P=0.045$) positive trend by the life table test (vehicle control, 1/50; low dose, 0/50; high dose, 4/50). The incidence in the high dose group was not significantly greater than that in the vehicle controls, and this lesion was not considered to be clearly compound related.

Incidences of nonfatal neoplasms in the thyroid gland of high dose male rats were significantly increased by the life table test but not by the incidental tumor test. The latter test is considered more appropriate, and thus, these incidences were considered not to be clearly compound related. C-Cell adenomas or carcinomas (combined)

in the thyroid gland of male rats were seen in 4/49 vehicle control, 4/50 low dose, and 5/49 high dose animals, and follicular cell adenomas or carcinomas (combined) in the thyroid gland were seen in 0/40 vehicle control, 2/50 low dose, and 3/49 high dose animals. Mesotheliomas in the tunica vaginalis, nonfatal tumors, were increased in dosed male rats, but the combined incidence of mesotheliomas at all sites was not significant by the incidental tumor test.

Two-Year Studies in Mice

In the 2-year studies, dimethyl methylphosphonate was administered to mice at doses of 0, 1,000, or 2,000 mg/kg. Deaths in high dose male mice between weeks 23 and 45 were associated with fighting. At week 45, 17 high dose male and 22 high dose female mice died from an apparent overdose that appeared to be due in part to improper resuspension of the dose mixture. Eleven low dose male mice died on the same day during week 77, and although the cause of death was not determined, it might also have been due partly to improper handling of the dose mixtures in the animal room. Lung congestion was seen in mice that died at weeks 45 and 77 but not in mice surviving to the end of the studies. Final survival in dosed groups of male mice was reduced, and the number of animals surviving to the end of the study was considered inadequate for carcinogenicity determination (final survival: vehicle control, 29/50; low dose, 12/50; high dose, 0/50). The number of high dose female mice surviving to the end of the study also was inadequate for a determination of carcinogenic activity (final survival: 41/50; 30/50; 2/50).

Mean body weights of high dose male mice were 7%-17% lower than those of vehicle control males between weeks 36 and 76, and those of high dose female mice were 6%-12% lower between weeks 88 and 103.

No increases in neoplastic lesions were considered to be compound related in male or female mice. In male mice, the incidences of hepatocellular adenomas or carcinomas (combined), lesions considered to be nonfatal, were significantly increased when assessed by the life table test but not by the incidental tumor test (vehicle control, 17/50; low dose, 21/50; high dose, 4/46); this finding was not considered to be compound related. The incidences of malignant lymphomas were increased in dosed male mice by the life table trend test (vehicle control, 7/50; low dose, 3/50; high dose 1/50); the low rate in the high dose group was due in part to decreased survival in this dose group. The incidences of lymphomas are considered not to be related to chemical administration. Dimethyl methylphosphonate caused increased incidences of hepatocytomegaly in dosed male mice (5/50; 17/50; 10/46).

Genetic Toxicology

Dimethyl methylphosphonate induced forward mutations in mouse lymphoma cells in the absence of metabolic activation, induced SCEs in CHO cells both with and without metabolic activation, gave limited evidence of clastogenicity in CHO cells in the absence of metabolic activation, and induced sex-linked recessive lethal mutations and translocations in Drosophila (Appendix E). Dimethyl methylphosphonate was negative in bacterial mutagenicity tests (Aerospace Medical Research Laboratory, 1983; Table E1). A dominant lethal effect was seen in male rats and mice (Dunnick et al., 1984a,b).

Other NTP Studies

The NTP has reported studies conducted on other nerve gas simulants nominated for study by the U.S. Army. Tris(2-ethylhexyl)phosphate was found to have equivocal evidence of carcinogenicity for male rats because of increased incidence of pheochromocytomas of the adrenal glands (NTP, 1984). There was no evidence of carcinogenicity for female F344/N rats or male $B6C3F_1$ mice. There was some evidence of carcinogenicity for female $B6C3F_1$ mice as shown by an increased incidence of hepatocellular carcinomas.

In the 2-year studies of dimethyl morpholinophosphoramidate, there was some evidence of carcinogenicity for male and female F344/N rats as indicated by increased incidences of mononuclear cell leukemia (NTP, 1986a). There was no evidence of carcinogenicity for male and female $B6C3F_1$ mice.

There was clear evidence of carcinogenicity for dimethyl hydrogen phosphite for male F344/N rats, as shown by increased incidences of lung and forestomach neoplasms (NTP, 1985a). There was equivocal evidence of carcinogenicity for female F344/N rats as shown by marginally increased incidences of lung and forestomach neoplasms. There was no evidence of carcinogenicity for male and female B6C3F$_1$ mice.

Data Audit

The experimental and tabulated data for the NTP Technical report on dimethyl methylphosphonate were examined for accuracy, consistency, and compliance with Good Laboratory Practice requirements (Appendix H). No discrepancies were found that influenced the final interpretation of the results of these studies.

Conclusions: Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of dimethyl methylphosphonate for male F344/N rats as shown by increased incidences of tubular cell hyperplasia, tubular cell adenocarcinomas, hyperplasia of the transitional cell epithelium, and transitional cell papillomas of the kidney. There was an increased incidence of mononuclear cell leukemia in male rats at 1,000 mg/kg. Renal toxicity and decreased survival occurred in dosed male rats. There was *no evidence of carcinogenic activity* of dimethyl methylphosphonate for female F344/N rats given doses of 500 or 1,000 mg/kg. The study in male B6C3F$_1$ mice was an *inadequate study of carcinogenic activity* because of decreased survival in both dosed groups. There was *no evidence of carcinogenic activity* for female B6C3F$_1$ mice receiving dimethyl methylphosphonate at 1,000 mg/kg; decreased survival of female mice at 2,000 mg/kg made this group inadequate for determination of carcinogenic activity.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 10.

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V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE

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TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma	2 (4%)		1 (2%)
Squamous cell carcinoma			1 (2%)
Keratoacanthoma		3 (6%)	
*Subcutaneous tissue	(50)	(50)	(50)
Neoplasm, benign, NOS	1 (2%)		
Sarcoma, NOS	1 (2%)	1 (2%)	
Fibroma	4 (8%)	3 (6%)	1 (2%)
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)		
Chondroma		1 (2%)	
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		1 (2%)	
Alveolar/bronchiolar carcinoma			2 (4%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	10 (20%)	10 (20%)	17 (34%)
#Spleen	(50)	(49)	(48)
Fibrosarcoma		1 (2%)	
Leukemia, mononuclear cell		1 (2%)	
#Lymph node	(49)	(49)	(48)
Pheochromocytoma, metastatic		1 (2%)	
#Thymus	(42)	(43)	(41)
Thymoma, benign		1 (2%)	
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Neurilemoma	1 (2%)		
DIGESTIVE SYSTEM			
*Palate	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)	1 (2%)	
*Tongue	(50)	(50)	(50)
Carcinoma, NOS			1 (2%)
#Salivary gland	(49)	(50)	(49)
Neurilemoma	1 (2%)		
#Liver	(50)	(49)	(49)
Neoplastic nodule	1 (2%)	4 (8%)	1 (2%)
#Pancreas	(49)	(49)	(49)
Adenocarcinoma, NOS	1 (2%)		
Acinar cell adenoma	2 (4%)	1 (2%)	2 (4%)
Pheochromocytoma, metastatic		1 (2%)	
#Forestomach	(50)	(48)	(47)
Papilloma, NOS		1 (2%)	
#Jejunum	(45)	(48)	(42)
Adenocarcinoma, NOS		1 (2%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Tubular cell adenocarcinoma		2 (4%)	3 (6%)
Lipoma	1 (2%)		
#Kidney/pelvis	(50)	(50)	(49)
Transitional cell papilloma		7 (14%)	3 (6%)
Transitional cell carcinoma		1 (2%)	
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(50)	(46)
Adenoma, NOS		1 (2%)	1 (2%)
#Anterior pituitary	(50)	(50)	(46)
Adenoma, NOS	13 (26%)	10 (20%)	7 (15%)
#Pituitary posterior	(50)	(50)	(46)
Pheochromocytoma, metastatic		1 (2%)	
#Adrenal medulla	(50)	(50)	(49)
Pheochromocytoma	12 (24%)	14 (28%)	18 (37%)
Pheochromocytoma, malignant		4 (8%)	
#Thyroid	(49)	(50)	(49)
Follicular cell adenoma			2 (4%)
Follicular cell carcinoma		2 (4%)	1 (2%)
C-cell adenoma	3 (6%)		1 (2%)
C-cell carcinoma	1 (2%)	4 (8%)	4 (8%)
#Parathyroid	(39)	(37)	(42)
Adenoma, NOS			1 (2%)
#Pancreatic islets	(49)	(49)	(49)
Islet cell adenoma	4 (8%)	3 (6%)	1 (2%)
Islet cell carcinoma	2 (4%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibroadenoma	1 (2%)	2 (4%)	
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS	2 (4%)		
Adenoma, NOS	1 (2%)	2 (4%)	
#Prostate	(47)	(49)	(47)
Adenoma, NOS	2 (4%)	3 (6%)	1 (2%)
#Testis	(50)	(50)	(49)
Interstitial cell tumor	41 (82%)	39 (78%)	39 (80%)
*Epididymis	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)		
*Scrotum	(50)	(50)	(50)
Mesothelioma, NOS			1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Astrocytoma	2 (4%)	1 (2%)	
#Cerebral cortex	(50)	(50)	(50)
Astrocytoma			1 (2%)
SPECIAL SENSE ORGANS			
*Ear canal	(50)	(50)	(50)
Papilloma, NOS			1 (2%)
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	
Squamous cell carcinoma			1 (2%)
Adenoma, NOS	1 (2%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
*Skull	(50)	(50)	(50)
Osteoma	1 (2%)		
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Pheochromocytoma, metastatic		1 (2%)	
*Mesentery	(50)	(50)	(50)
Lipoma		2 (4%)	
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS		4 (8%)	6 (12%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic	1 (2%)		
Mesothelioma, NOS	1 (2%)	1 (2%)	
Mesothelioma, malignant	1 (2%)		
Tail			
Squamous cell papilloma	1		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	18	24	27
Moribund sacrifice	5	9	18
Terminal sacrifice	26	17	4
Dosing accident	1		1
TUMOR SUMMARY			
Total animals with primary tumors**	46	45	43
Total primary tumors	117	133	118
Total animals with benign tumors	45	44	43
Total benign tumors	93	95	79
Total animals with malignant tumors	18	23	28
Total malignant tumors	21	29	31
Total animals with secondary tumors ##	1	1	
Total secondary tumors	1	4	
Total animals with tumors uncertain--benign or malignant	3	7	7
Total uncertain tumors	3	9	8

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE: VEHICLE CONTROL

ANIMAL NUMBER	0 3 8	0 1 8	0 1 7	0 4 1	0 4 3	0 0 5	0 0 8	0 1 1	0 2 7	0 0 1	0 0 8	0 4 8	0 3 3	0 3 6	0 0 9	0 3 7	0 4 6	0 1 6	0 3 4	0 4 5	0 4 7	0 1 3	0 3 5	0 0 2	0 0 4
WEEKS ON STUDY	0 3 5	0 5 1	0 5 5	0 5 7	0 5 7	0 5 8	0 5 8	0 6 3	0 6 5	0 6 7	0 7 4	0 8 3	0 8 8	0 9 1	0 9 6	0 9 8	0 9 9	0 9 9	1 0 0	1 0 0	1 0 2	1 0 4	1 0 5	1 0 5
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplasm, benign, NOS																							X		
Sarcoma, NOS																									
Fibroma														X										X	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	N	N	N	N	N	N	N	N	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+
Squamous cell carcinoma													X												
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	–	+	+	+	–	–	+	+	+	+	–	–	+	+	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma																									
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																							X		
Salivary gland	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma															X										
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																							X		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Adenocarcinoma, NOS																X									
Acinar cell adenoma						X																			
Esophagus	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	–	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	–	+	+	–	+	+
Large intestine	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Urinary bladder	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	–	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS															X	X	X	X				X			X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma			X			X								X							X	X			
Thyroid	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																									
C-cell carcinoma																									
Parathyroid	–	–	+	+	+	+	–	–	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Islet cell adenoma														X					X						
Islet cell carcinoma																		X							
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor							X		X	X	X	X	X	X	X	X			X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	–	–	+	+	+	+	–	+	+
Adenoma, NOS																									
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS				X																					
Adenoma, NOS																									
Epididymis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS																X									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																									
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS													X												
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS, metastatic																X									
Mesothelioma, NOS																									
Mesothelioma, malignant																X									
Leukemia, mononuclear cell														X				X	X	X	X	X			
Tail																									
Squamous cell papilloma																									

+: Tissue examined microscopically
–: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no macroscopic examination
S: Animal missexed
.: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

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TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL
(Continued)

ANIMAL NUMBER	007	010	012	014	015	019	020	021	022	023	024	025	026	028	029	030	031	032	033	039	040	042	044	049	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma									X													X				2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Neoplasm, benign, NOS																										1
Sarcoma, NOS												X														1
Fibroma								X																	X	4
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma							X																			1
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neurilemoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS																										1
Acinar cell adenoma																	X									2
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma										X																1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X	X				X		X		X								X	X							13
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma				X	X			X				X				X		X			X					12
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell adenoma										X						X					X					3
C-cell carcinoma																			X							1
Parathyroid	+	+	+	+	+	–	+	–	+	+	+	+	+	–	+	–	+	+	+	+	–	+	+	+	+	39
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma												X						X								4
Islet cell carcinoma	X																									2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	*50
Fibroadenoma																		X								1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	41
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS						X												X								2
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS	X																									2
Adenoma, NOS																					X					1
Epididymis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma								X		X																2
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteoma																							X			1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS, metastatic																						X				1
Mesothelioma, NOS																										1
Mesothelioma, malignant				X																						1
Leukemia, mononuclear cell												X		X	X											10
Tail																										
Squamous cell papilloma			X																							1

* Animals necropsied

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TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE: LOW DOSE

ANIMAL NUMBER	020	008	032	044	045	018	007	021	038	014	031	048	030	027	011	052	010	024	033	009	029	038	017	023	049
WEEKS ON STUDY	041	049	054	055	058	059	059	060	063	063	067	070	073	076	078	079	082	083	085	086	088	088	088	088	
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																							X		
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	N	N	N	N	N	N	N	N	N	N	N	N	+	+	+	N	+	+	+	+	+	+	+	+	+
Chondroma																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Leukemia, mononuclear cell													X												
Lymph nodes	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma, metastatic																						X			
Thymus	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	–	+	+	+	+	+	+	+
Thymoma, benign																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																			X						
Bile duct	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Pheochromocytoma, metastatic																						X			
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																									
Small intestine	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Large intestine	+	+	+	+	+	–	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																									
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																									
Transitional cell carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	–	–	+	–	+	+	–	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS											X											X			
Pheochromocytoma, metastatic																						X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma													X				X						X		
Pheochromocytoma, malignant																						X			
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
C-cell carcinoma																									
Parathyroid	+	–	+	+	–	+	–	–	+	+	–	–	+	+	+	+	+	+	+	+	+	–	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma						X				X						X									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	+	N	+	+	+	N	+	+	N	N	+	N	+	+	+	+	+	+	+	+
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor		X			X			X		X	X		X	X	X		X	X	X	X	X		X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Adenoma, NOS																			X						
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																									
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pheochromocytoma, metastatic																						X			
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																			X						
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Lipoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS																									
Leukemia, mononuclear cell										X		X				X				X				X	

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TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	0 4 9	0 4 1	0 0 3	0 3 5	0 3 7	0 4 3	0 0 4	0 1 6	0 0 5	0 0 9	0 1 1	0 1 2	0 1 3	0 1 5	0 1 9	0 2 2	0 2 5	0 2 6	0 2 8	0 3 0	0 3 4	0 3 9	0 4 0	0 4 2	0 4 7	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	0 8 8	0 9 3	0 9 8	0 9 8	0 9 8	0 9 9	1 0 0	1 0 1	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma				X											X											3
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS						X																				1
Fibroma							X														X			X		3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X																									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	47
Nasal cavity	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Chondroma																				X						1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma											X															1
Leukemia, mononuclear cell																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma, metastatic																										1
Thymus	+	+	+	–	+	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Thymoma, benign	X																									1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma			X																							1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule										X		X						X								4
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar cell adenoma																								X		1
Pheochromocytoma, metastatic																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papilloma, NOS																							X			1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, NOS											X															1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma	X																					X				2
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell papilloma						X				X					X		X				X		X	X		7
Transitional cell carcinoma																				X						1
Urinary bladder	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X	X		X		X		X							X	X					X		X			11
Pheochromocytoma, metastatic																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma	X			X		X				X		X	X					X		X	X		X	X		14
Pheochromocytoma, malignant			X									X			X											4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma																		X							X	2
C-cell carcinoma	X										X					X							X			4
Parathyroid	–	+	+	+	+	–	+	+	+	+	+	+	–	+	+	–	+	–	+	+	+	–	+	+	+	37
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																										3
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma											X		X													2
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	39
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS								X												X						3
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS										X				X												2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma					X																					1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS								X																		1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pheochromocytoma, metastatic																										1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS											X				X				X							4
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Lipoma				X		X																				2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS												X														1
Leukemia, mononuclear cell		X										X						X			X	X				10

* Animals necropsied

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TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE: HIGH DOSE

ANIMAL NUMBER	0171	0281	0421	0471	0151	0001	0321	0225	0366	0377	0433	0500	0122	0440	0092	0244	0066	0455	0110	0093	0088	0268	0499	0209	0334
WEEKS ON STUDY	0233	0534	0553	0557	0597	0559	0599	0665	0665	0685	0668	0688	0699	0712	0768	0768	0777	0777	0778	0799	0799	0799	0799	0833	0883
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma													X												
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Trachea	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
Thymus	+	-	-	-	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Salivary gland	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	-	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
Stomach	+	-	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
Small intestine	-	-	+	+	-	+	+	-	-	-	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+
Large intestine	+	-	+	-	+	+	+	+	+	+	+	+	+	-	-	+	-	+	-	-	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																		X	X						
Kidney/pelvis	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																									
Urinary bladder	+	-	+	+	+	+	+	-	-	-	+	+	+	+	-	+	+	+	+	+	+	+	-	+	-
ENDOCRINE SYSTEM																									
Pituitary	-	-	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS									X								X							X	
Adrenal	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma							X						X		X							X		X	
Thyroid	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma																									
C-cell adenoma																									
C-cell carcinoma																					X				
Parathyroid	+	-	+	+	-	-	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Pancreatic islets	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	+	N	+	+	+	+	+	+	N	+	N	N	N	+	+	+	+	+	N	+	+
Testis	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor								X	X		X	X	X	X		X		X	X	X	X	X	X	X	X
Prostate	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																									
SPECIAL SENSE ORGANS																									
Ear	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papilloma, NOS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma																									
BODY CAVITIES																									
Tunica vaginalis	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS												X			X		X								
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell															X	X						X		X	X
Scrotum, NOS																									
Mesothelioma, NOS												X													

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TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	0030	0022	0039	0048	0004	0029	0016	0011	0013	0014	0005	0023	0046	0027	0031	0009	0019	0018	0007	0021	0044	0033	0035	0038	0041	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	0884	0885	0885	0885	0886	0886	0887	0888	0888	0888	0889	0889	0889	0890	0900	0908	0999	1000	1011	1011	1011	1055	1055	1055	1055	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																			X							1
Squamous cell carcinoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma														X												1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma				X														X								2
Trachea	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	–	+	+	+	+	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS											X															1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule																									X	1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar cell adenoma																X									X	2
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	42
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tubular cell adenocarcinoma																			X							3
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional cell papilloma		X	X													X										3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	41
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma, NOS					X									X			X		X						X	6
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma							X	X	X	X			X		X	X	X	X		X		X	X	X		18
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma											X							X								2
Follicular cell carcinoma										X																1
C-cell adenoma											X															1
C-cell carcinoma								X																X	X	4
Parathyroid	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	42
Adenoma, NOS		X																								1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																		X								1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	N	+	N	N	+	+	+	+	N	+	+	N	+	+	+	+	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	39
Prostate	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS				X																						1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma														X												1
SPECIAL SENSE ORGANS																										
Ear	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papilloma, NOS	X																									1
Zymbal gland	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma	X																									1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS					X													X		X						6
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell							X		X			X	X	X			X	X			X	X	X	X	X	17
Scrotum, NOS																										1
Mesothelioma, NOS																										

* Animals necropsied

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TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE

	Vehicle Control	500 mg/kg	1,000 mg/kg
Skin: Keratoacanthoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	13.2%	0.0%
Terminal Rates (c)	0/27 (0%)	1/17 (6%)	0/4 (0%)
Week of First Observation		88	
Life Table Tests (d)	P=0.322	P=0.065	(e)
Incidental Tumor Tests (d)	P=0.637	P=0.129	(e)
Cochran-Armitage Trend Test (d)	P=0.640		
Fisher Exact Test (d)		P=0.121	(e)
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	4/50 (8%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	13.5%	16.4%	8.3%
Terminal Rates (c)	3/27 (11%)	2/17 (12%)	0/4 (0%)
Week of First Observation	91	100	90
Life Table Tests (d)	P=0.497	P=0.565	P=0.664
Incidental Tumor Tests (d)	P=0.283N	P=0.622N	P=0.189N
Cochran-Armitage Trend Test (d)	P=0.133N		
Fisher Exact Test (d)		P=0.500N	P=0.181N
Subcutaneous Tissue: Fibroma or Sarcoma			
Overall Rates (a)	5/50 (10%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	17.1%	20.6%	8.3%
Terminal Rates (c)	4/27 (15%)	2/17 (12%)	0/4 (0%)
Week of First Observation	91	99	90
Life Table Tests (d)	P=0.523	P=0.491	P=0.707
Incidental Tumor Tests (d)	P=0.244N	P=0.626	P=0.164N
Cochran-Armitage Trend Test (d)	P=0.080N		
Fisher Exact Test (d)		P=0.500N	P=0.102N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	10/50 (20%)	11/50 (22%)	17/50 (34%)
Adjusted Rates (b)	30.0%	38.5%	100.0%
Terminal Rates (c)	4/27 (15%)	4/17 (24%)	4/4 (100%)
Week of First Observation	91	63	76
Life Table Tests (d)	P<0.001	P=0.188	P<0.001
Incidental Tumor Tests (d)	P=0.048	P=0.493	P=0.032
Cochran-Armitage Trend Test (d)	P=0.068		
Fisher Exact Test (d)		P=0.500	P=0.088
Liver: Neoplastic Nodule			
Overall Rates (a)	1/50 (2%)	4/49 (8%)	1/49 (2%)
Adjusted Rates (b)	3.7%	20.2%	25.0%
Terminal Rates (c)	1/27 (4%)	3/17 (18%)	1/4 (25%)
Week of First Observation	105	82	105
Life Table Tests (d)	P=0.104	P=0.079	P=0.302
Incidental Tumor Tests (d)	P=0.188	P=0.122	P=0.302
Cochran-Armitage Trend Test (d)	P=0.593		
Fisher Exact Test (d)		P=0.175	P=0.748
Kidney: Transitional Cell Papilloma			
Overall Rates (a)	0/50 (0%)	7/50 (14%)	3/49 (6%)
Adjusted Rates (b)	0.0%	38.5%	17.5%
Terminal Rates (c)	0/27 (0%)	6/17 (35%)	0/4 (0%)
Week of First Observation		99	85
Life Table Tests (d)	P=0.001	P<0.001	P=0.031
Incidental Tumor Tests (d)	P=0.014	P=0.001	P=0.301
Cochran-Armitage Trend Test (d)	P=0.151		
Fisher Exact Test (d)		P=0.006	P=0.117

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Kidney: Transitional Cell Papilloma or Carcinoma			
Overall Rates (a)	0/50 (0%)	8/50 (16%)	3/49 (6%)
Adjusted Rates (b)	0.0%	44.1%	17.5%
Terminal Rates (c)	0/27 (0%)	7/17 (41%)	0/4 (0%)
Week of First Observation		99	85
Life Table Tests (d)	P<0.001	P<0.001	P=0.031
Incidental Tumor Tests (d)	P=0.010	P<0.001	P=0.301
Cochran-Armitage Trend Test (d)	P=0.161		
Fisher Exact Test (d)		P=0.003	P=0.117
Kidney: Tubular Cell Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	2/50 (4%)	3/49 (6%)
Adjusted Rates (b)	0.0%	9.2%	19.4%
Terminal Rates (c)	0/27 (0%)	1/17 (6%)	0/4 (0%)
Week of First Observation		88	77
Life Table Tests (d)	P=0.014	P=0.160	P=0.043
Incidental Tumor Tests (d)	P=0.091	P=0.288	P=0.167
Cochran-Armitage Trend Test (d)	P=0.079		
Fisher Exact Test (d)		P=0.247	P=0.117
Pituitary Gland: Adenoma			
Overall Rates (a)	13/50 (26%)	10/50 (20%)	7/46 (15%)
Adjusted Rates (b)	39.6%	38.5%	46.9%
Terminal Rates (c)	8/27 (30%)	3/17 (18%)	1/4 (25%)
Week of First Observation	96	63	65
Life Table Tests (d)	P=0.126	P=0.426	P=0.101
Incidental Tumor Tests (d)	P=0.319N	P=0.539N	P=0.516N
Cochran-Armitage Trend Test (d)	P=0.119N		
Fisher Exact Test (d)		P=0.318N	P=0.148N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	12/50 (24%)	14/50 (28%)	18/49 (37%)
Adjusted Rates (b)	35.5%	57.8%	91.3%
Terminal Rates (c)	7/27 (26%)	8/17 (47%)	3/4 (75%)
Week of First Observation	55	70	65
Life Table Tests (d)	P<0.001	P=0.092	P<0.001
Incidental Tumor Tests (d)	P=0.022	P=0.284	P=0.071
Cochran-Armitage Trend Test (d)	P=0.101		
Fisher Exact Test (d)		P=0.410	P=0.123
Adrenal Gland: Malignant Pheochromocytoma			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	0/49 (0%)
Adjusted Rates (b)	0.0%	18.5%	0.0%
Terminal Rates (c)	0/27 (0%)	2/17 (12%)	0/4 (0%)
Week of First Observation		86	
Life Table Tests (d)	P=0.236	P=0.026	(e)
Incidental Tumor Tests (d)	P=0.486	P=0.052	(e)
Cochran-Armitage Trend Test (d)	P=0.316		
Fisher Exact Test (d)		P=0.059	(e)
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	12/50 (24%)	18/50 (36%)	18/49 (37%)
Adjusted Rates (b)	35.5%	69.7%	91.3%
Terminal Rates (c)	7/27 (26%)	10/17 (59%)	3/4 (75%)
Week of First Observation	55	70	65
Life Table Tests (d)	P<0.001	P=0.012	P<0.001
Incidental Tumor Tests (d)	P=0.017	P=0.069	P=0.071
Cochran-Armitage Trend Test (d)	P=0.105		
Fisher Exact Test (d)		P=0.136	P=0.123

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	0/49 (0%)	2/50 (4%)	3/49 (6%)
Adjusted Rates (b)	0.0%	11.8%	22.9%
Terminal Rates (c)	0/27 (0%)	2/17 (12%)	0/4 (0%)
Week of First Observation		105	88
Life Table Tests (d)	P=0.003	P=0.143	P=0.014
Incidental Tumor Tests (d)	P=0.050	P=0.143	P=0.301
Cochran-Armitage Trend Test (d)	P=0.081		
Fisher Exact Test (d)		P=0.253	P=0.121
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	3/49 (6%)	0/50 (0%)	1/49 (2%)
Adjusted Rates (b)	11.1%	0.0%	6.7%
Terminal Rates (c)	3/27 (11%)	0/17 (0%)	0/4 (0%)
Week of First Observation	105		89
Life Table Tests (d)	P=0.567N	P=0.212N	P=0.596
Incidental Tumor Tests (d)	P=0.317N	P=0.212N	P=0.643N
Cochran-Armitage Trend Test (d)	P=0.175N		
Fisher Exact Test (d)		P=0.117N	P=0.309N
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	1/49 (2%)	4/50 (8%)	4/49 (8%)
Adjusted Rates (b)	3.7%	20.6%	54.3%
Terminal Rates (c)	1/27 (4%)	3/17 (18%)	2/4 (50%)
Week of First Observation	105	88	79
Life Table Tests (d)	P=0.002	P=0.075	P=0.004
Incidental Tumor Tests (d)	P=0.022	P=0.122	P=0.030
Cochran-Armitage Trend Test (d)	P=0.145		
Fisher Exact Test (d)		P=0.187	P=0.181
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	4/49 (8%)	4/50 (8%)	5/49 (10%)
Adjusted Rates (b)	14.8%	20.6%	57.3%
Terminal Rates (c)	4/27 (15%)	3/17 (18%)	2/4 (50%)
Week of First Observation	105	88	79
Life Table Tests (d)	P=0.008	P=0.387	P=0.008
Incidental Tumor Tests (d)	P=0.112	P=0.486	P=0.118
Cochran-Armitage Trend Test (d)	P=0.429		
Fisher Exact Test (d)		P=0.631N	P=0.500
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	4/49 (8%)	3/49 (6%)	1/49 (2%)
Adjusted Rates (b)	12.6%	7.3%	12.5%
Terminal Rates (c)	2/27 (7%)	0/17 (0%)	0/4 (0%)
Week of First Observation	91	58	100
Life Table Tests (d)	P=0.434N	P=0.647N	P=0.678
Incidental Tumor Tests (d)	P=0.112N	P=0.400N	P=0.289N
Cochran-Armitage Trend Test (d)	P=0.133N		
Fisher Exact Test (d)		P=0.500N	P=0.181N
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	6/49 (12%)	3/49 (6%)	1/49 (2%)
Adjusted Rates (b)	18.8%	7.3%	12.5%
Terminal Rates (c)	3/27 (11%)	0/17 (0%)	0/4 (0%)
Week of First Observation	91	58	100
Life Table Tests (d)	P=0.259N	P=0.425N	P=0.606N
Incidental Tumor Tests (d)	P=0.042N	P=0.203N	P=0.153N
Cochran-Armitage Trend Test (d)	P=0.036N		
Fisher Exact Test (d)		P=0.243N	P=0.056N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	9.4%	11.8%	0.0%
Terminal Rates (c)	2/27 (7%)	2/17 (12%)	0/4 (0%)
Week of First Observation	57	105	
Life Table Tests (d)	P=0.350N	P=0.669N	P=0.356N
Incidental Tumor Tests (d)	P=0.293N	P=0.622N	P=0.261N
Cochran-Armitage Trend Test (d)	P=0.082N		
Fisher Exact Test (d)		P=0.500N	P=0.121N
Prostate: Adenoma			
Overall Rates (a)	2/47 (4%)	3/49 (6%)	1/47 (2%)
Adjusted Rates (b)	7.4%	13.9%	4.2%
Terminal Rates (c)	2/27 (7%)	1/17 (6%)	0/4 (0%)
Week of First Observation	105	82	85
Life Table Tests (d)	P=0.360	P=0.319	P=0.585
Incidental Tumor Tests (d)	P=0.465N	P=0.472	P=0.730N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test (d)		P=0.520	P=0.500N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	41/50 (82%)	39/50 (78%)	39/49 (80%)
Adjusted Rates (b)	100.0%	97.4%	100.0%
Terminal Rates (c)	27/27 (100%)	16/17 (94%)	4/4 (100%)
Week of First Observation	58	49	65
Life Table Tests (d)	P<0.001	P=0.028	P<0.001
Incidental Tumor Tests (d)	P=0.283	P=0.512	P=0.320
Cochran-Armitage Trend Test (d)	P=0.430N		
Fisher Exact Test (d)		P=0.402N	P=0.480N
Tunica Vaginalis: Mesothelioma			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	6/50 (12%)
Adjusted Rates (b)	0.0%	20.2%	34.3%
Terminal Rates (c)	0/27 (0%)	3/17 (18%)	0/4 (0%)
Week of First Observation		82	68
Life Table Tests (d)	P<0.001	P=0.025	P=0.002
Incidental Tumor Tests (d)	P=0.007	P=0.044	P=0.046
Cochran-Armitage Trend Test (d)	P=0.014		
Fisher Exact Test (d)		P=0.059	P=0.013
All Sites: Mesothelioma			
Overall Rates (a)	(f) 2/50 (4%)	5/50 (10%)	6/50 (12%)
Adjusted Rates (b)	6.4%	25.9%	34.3%
Terminal Rates (c)	1/27 (4%)	4/17 (24%)	0/4 (0%)
Week of First Observation	96	82	68
Life Table Tests (d)	P=0.002	P=0.083	P=0.009
Incidental Tumor Tests (d)	P=0.034	P=0.130	P=0.141
Cochran-Armitage Trend Test (d)	P=0.107		
Fisher Exact Test (d)		P=0.218	P=0.134

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 1,000 mg/kg and vehicle control groups.
(f) Includes one malignant mesothelioma

TABLE A4a. HISTORICAL INCIDENCE OF RENAL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	No. Examined	No. of Tumors	Diagnosis
Transitional Cell			
Historical Incidence at Litton Bionetics, Inc.			
No renal transitional cell tumors have been observed in 450 corn oil vehicle control male rats.			
Overall Historical Incidence	1,448	1 (<0.1%)	Transitional cell papilloma
Tubular Cell			
Historical Incidence at Litton Bionetics, Inc.			
	450	(b) 2	Tubular cell adenoma
		(c) 1	Adenocarcinoma, NOS
	Total	3 (0.7%)	
Overall Historical Incidence			
		3	Tubular cell adenoma
		2	Adenocarcinoma, NOS
		3	Tubular cell adenocarcinoma
	Total	8 (0.6%)	

(a) Data as of August 30, 1985, for studies of at least 104 weeks. No more than one tumor was observed in any vehicle control group.
(b) Observed in the dimethylvinyl chloride and 4-vinylcyclohexene studies
(c) Observed in the 2,4-toluene diisocyanate study

TABLE A4b. HISTORICAL INCIDENCE OF LEUKEMIA IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls
Historical Incidence at Litton Bionetics, Inc.	
Diallyl phthalate	13/50
Dimethyl morpholinophosphoramidate	14/50
Tris(2-ethylhexyl)phosphate	2/50
Dimethyl hydrogen phosphite	9/50
Dimethylvinyl chloride	3/50
3-Chloro-2-methylpropene	9/50
4-Vinylcyclohexene	14/50
Dimethyl methylphosphonate	10/50
2,4-Toluene diisocyanate	11/50
TOTAL	85/450 (18.9%)
SD (b)	8.78%
Range (c)	
High	14/50
Low	2/50
Overall Historical Incidence at All Laboratories	
TOTAL	202/1,450 (13.9%)
SD (b)	7.55%
Range (c)	
High	14/50
Low	1/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4c. HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Pheochromocytoma	Malignant Pheochromocytoma	Pheochromocytoma or Malignant Pheochromocytoma
Historical Incidence at Litton Bionetics, Inc.			
Diallyl phthalate	13/50	0/50	13/50
Dimethyl morpholinophosphoramidate	9/49	0/49	9/49
Tris(2-ethylhexyl)phosphate	2/50	0/50	2/50
Dimethyl hydrogen phosphite	6/50	0/50	6/50
Dimethylvinyl chloride	11/50	2/50	13/50
3-Chloro-2-methylpropene	14/50	0/50	14/50
4-Vinylcyclohexene	17/50	0/50	17/50
Dimethyl methylphosphonate	12/50	0/50	12/50
2,4-Toluene diisocyanate	12/50	0/50	12/50
TOTAL	96/449 (21.4%)	2/449 (0.4%)	98/449 (21.8%)
SD (b)	8.93%	1.33%	9.06%
Range (c)			
High	17/50	2/50	17/50
Low	2/50	0/50	2/50
Overall Historical Incidence			
TOTAL	338/1,442 (23.4%)	13/1,442 (0.9%)	347/1,442 (24.1%)
SD (b)	8.72%	1.27%	8.66%
Range (c)			
High	20/49	2/50	20/49
Low	2/50	0/50	2/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4d. HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Litton Bionetics, Inc.			
Diallyl phthalate	0/49	0/49	0/49
Dimethyl morpholinophosphoramidate	2/50	0/50	2/50
Tris(2-ethylhexyl)phosphate	0/46	1/46	1/46
Dimethyl hydrogen phosphite	0/50	2/50	2/50
Dimethylvinyl chloride	1/50	0/50	1/50
3-Chloro-2-methylpropene	0/49	0/49	0/49
4-Vinylcyclohexene	0/48	0/48	0/48
Dimethyl methylphosphonate	0/49	0/49	0/49
2,4-Toluene diisocyanate	0/46	0/46	0/46
TOTAL	3/437 (0.7%)	3/437 (0.7%)	6/437 (1.4%)
SD (b)	1.41%	1.44%	1.74%
Range (c)			
High	2/50	2/50	2/50
Low	0/50	0/50	0/49
Overall Historical Incidence			
TOTAL	(d) 15/1,417 (1.1%)	20/1,417 (1.4%)	(d) 35/1,417 (2.5%)
SD (b)	1.92%	1.95%	2.66%
Range (c)			
High	4/49	4/50	5/50
Low	0/50	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes one cystadenoma, NOS

TABLE A4e. HISTORICAL INCIDENCE OF MESOTHELIOMAS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls	
	Tunica Vaginalis	All Sites Combined
Historical Incidence at Litton Bionetics, Inc.		
Diallyl phthalate	0/50	1/50
Dimethyl morpholinophosphoramidate	0/50	1/50
Tris(2-ethylhexyl)phosphate	2/50	2/50
Dimethyl hydrogen phosphite	0/50	6/50
Dimethylvinyl chloride	0/50	2/50
3-Chloro-2-methylpropene	1/50	1/50
4-Vinylcyclohexene	2/50	3/50
Dimethyl methylphosphonate	0/50	2/50
2,4-Toluene diisocyanate	0/50	2/50
TOTAL	5/450 (1.1%)	20/450 (4.4%)
SD (b)	1.76%	3.13%
Range (c)		
High	2/50	6/50
Low	0/50	1/50
Overall Historical Incidence		
TOTAL	24/1,450 (1.7%)	55/1,450 (3.8%)
SD (b)	2.27%	2.74%
Range (c)		
High	3/50	6/50
Low	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks; includes mesothelioma, NOS, benign and malignant.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4f. HISTORICAL INCIDENCE OF THYROID GLAND C-CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Litton Bionetics, Inc.			
Diallyl phthalate	2/49	0/49	2/49
Dimethyl morpholinophosphoramidate	4/50	0/50	4/50
Tris(2-ethylhexyl)phosphate	4/46	2/46	6/46
Dimethyl hydrogen phosphite	2/50	2/50	4/50
Dimethylvinyl chloride	3/50	2/50	5/50
3-Chloro-2-methylpropene	3/49	4/49	7/49
4-Vinylcyclohexene	4/48	0/48	4/48
Dimethyl methylphosphonate	3/49	1/49	4/49
2,4-Toluene diisocyanate	2/46	1/46	3/46
TOTAL	27/437 (6.2%)	12/437 (2.7%)	39/437 (8.9%)
SD (b)	1.83%	2.70%	3.14%
Range (c)			
High	4/46	4/49	7/49
Low	2/50	0/50	2/49
Overall Historical Incidence			
TOTAL	125/1,417 (8.8%)	59/1,417 (4.2%)	181/1,417 (12.8%)
SD (b)	5.55%	3.24%	6.36%
Range (c)			
High	10/49	6/50	12/49
Low	0/50	0/50	2/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)		
Hyperkeratosis			2 (4%)
Acanthosis			2 (4%)
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Foreign body, NOS			1 (2%)
Inflammation, serous			1 (2%)
Inflammation, suppurative	7 (14%)	9 (18%)	7 (14%)
Inflammation, acute focal	1 (2%)		
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic		1 (2%)	1 (2%)
Inflammation, chronic focal			1 (2%)
Reaction, foreign body		1 (2%)	2 (4%)
Inflammation, pyogranulomatous	3 (6%)		1 (2%)
Granuloma, pyogenic			1 (2%)
Infection, fungal			1 (2%)
Polyp, NOS		1 (2%)	
Metaplasia, squamous			1 (2%)
#Trachea	(50)	(47)	(48)
Inflammation, chronic			1 (2%)
Inflammation, chronic focal		1 (2%)	2 (4%)
#Lung/bronchus	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		1 (2%)
Reaction, foreign body			1 (2%)
#Lung	(50)	(50)	(50)
Congestion, NOS	7 (14%)	9 (18%)	7 (14%)
Edema, NOS		1 (2%)	
Hemorrhage	1 (2%)		
Bronchopneumonia, NOS			1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)	1 (2%)	7 (14%)
Inflammation, interstitial	2 (4%)	1 (2%)	1 (2%)
Inflammation, suppurative			1 (2%)
Pneumonia, interstitial chronic	1 (2%)		
Inflammation, chronic focal	7 (14%)	2 (4%)	4 (8%)
Inflammation, granulomatous focal		1 (2%)	
Granuloma, foreign body			1 (2%)
Reaction, foreign body		1 (2%)	
Calcification, focal			1 (2%)
Hyperplasia, adenomatous			1 (2%)
Hyperplasia, alveolar epithelium	2 (4%)		2 (4%)
#Lung/alveoli	(50)	(50)	(50)
Histiocytosis	10 (20%)	8 (16%)	3 (6%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(49)	(49)
Hemorrhage		1 (2%)	
Inflammation, granulomatous focal			1 (2%)
Fibrosis, focal		1 (2%)	
Necrosis, focal		1 (2%)	
Hypoplasia, NOS		1 (2%)	
Mastocytosis			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Spleen	(50)	(49)	(48)
Fibrosis	1 (2%)	2 (4%)	1 (2%)
Fibrosis, focal	1 (2%)	1 (2%)	1 (2%)
Necrosis, NOS	1 (2%)	1 (2%)	
Hemosiderosis		1 (2%)	
Depletion, lymphoid		1 (2%)	
Hyperplasia, stromal	1 (2%)	1 (2%)	
#Lymph node	(49)	(49)	(48)
Plasmacytosis		1 (2%)	
#Mandibular lymph node	(49)	(49)	(48)
Dilatation/sinus		1 (2%)	
Plasmacytosis			1 (2%)
Hyperplasia, lymphoid			1 (2%)
#Mediastinal lymph node	(49)	(49)	(48)
Hemorrhage		1 (2%)	
Plasmacytosis		1 (2%)	
Mastocytosis		2 (4%)	
#Mesenteric lymph node	(49)	(49)	(48)
Congestion, NOS		1 (2%)	
Hemorrhage		1 (2%)	
#Ileum	(45)	(48)	(42)
Hyperplasia, lymphoid	1 (2%)		
#Adrenal	(50)	(50)	(49)
Hematopoiesis	1 (2%)		
#Thymus	(42)	(43)	(41)
Hemorrhage			1 (2%)
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Inflammation, chronic focal			1 (2%)
#Heart/atrium	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)	1 (2%)	1 (2%)
Thrombus, organized	1 (2%)		
#Myocardium	(50)	(50)	(50)
Degeneration, NOS	39 (78%)	37 (74%)	40 (80%)
Necrosis, focal	1 (2%)		1 (2%)
*Blood vessel	(50)	(50)	(50)
Periarteritis	1 (2%)		
Calcification, NOS	1 (2%)		
*Pulmonary artery	(50)	(50)	(50)
Calcification, NOS			1 (2%)
Calcification, focal	9 (18%)	9 (18%)	7 (14%)
#Pancreas	(49)	(49)	(49)
Periarteritis		1 (2%)	1 (2%)
DIGESTIVE SYSTEM			
#Parotid gland	(49)	(50)	(49)
Inflammation, suppurative			1 (2%)
Necrosis, focal		1 (2%)	
Atrophy, NOS			1 (2%)
#Liver	(50)	(49)	(49)
Hernia, NOS	2 (4%)	2 (4%)	4 (8%)
Dilatation/sinus		2 (4%)	
Congestion, NOS			2 (4%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
#Liver (Continued)	(50)	(49)	(49)
Hemorrhage		2 (4%)	
Inflammation, chronic focal	2 (4%)	3 (6%)	1 (2%)
Inflammation, granulomatous			1 (2%)
Degeneration, lipoid	2 (4%)		
Necrosis, focal	2 (4%)		1 (2%)
Lipoidosis	2 (4%)	1 (2%)	
Basophilic cyto change	2 (4%)		
Ground glass cyto change	4 (8%)	3 (6%)	
Focal cellular change	1 (2%)		1 (2%)
Eosinophilic cyto change	1 (2%)	4 (8%)	
Clear cell change	5 (10%)		
Regeneration, NOS	4 (8%)		
#Liver/caudate lobe	(50)	(49)	(49)
Infarct, NOS		1 (2%)	
#Liver/centrilobular	(50)	(49)	(49)
Dilatation/sinus		1 (2%)	
Necrosis, NOS	2 (4%)	1 (2%)	
Lipoidosis	3 (6%)		
#Liver/periportal	(50)	(49)	(49)
Inflammation, chronic			1 (2%)
Degeneration, lipoid		1 (2%)	1 (2%)
Necrosis, NOS		1 (2%)	
Lipoidosis	1 (2%)	1 (2%)	
#Liver/hepatocytes	(50)	(49)	(49)
Hypertrophy, focal			1 (2%)
Regeneration, NOS		1 (2%)	
#Bile duct	(50)	(49)	(49)
Retention of content		1 (2%)	
Cyst, NOS			1 (2%)
Hyperplasia, NOS	40 (80%)	39 (80%)	31 (63%)
#Pancreas	(49)	(49)	(49)
Inflammation, chronic focal			1 (2%)
#Pancreatic duct	(49)	(49)	(49)
Hyperplasia, focal		1 (2%)	
Hyperplasia, cystic	1 (2%)		
#Pancreatic acinus	(49)	(49)	(49)
Necrosis, focal		1 (2%)	
Atrophy, NOS	1 (2%)	1 (2%)	2 (4%)
Atrophy, focal	6 (12%)	9 (18%)	4 (8%)
Hyperplasia, focal	6 (12%)	4 (8%)	4 (8%)
#Stomach	(50)	(48)	(47)
Inflammation, acute/chronic			1 (2%)
#Glandular stomach	(50)	(48)	(47)
Dilatation, NOS			1 (2%)
Ulcer, NOS	1 (2%)		
Necrosis, focal	1 (2%)		
Calcification, focal	1 (2%)		
#Forestomach	(50)	(48)	(47)
Ulcer, NOS		1 (2%)	2 (4%)
Inflammation, acute focal	1 (2%)		
Inflammation, acute/chronic		1 (2%)	
Hyperplasia, epithelial		2 (4%)	5 (11%)
[illegible]plasia, epithelial		1 (2%)	
#D[illegible]enum	(45)	(48)	(42)
[illegible]ectopia	1 (2%)		
Inflammation, chronic			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Duodenal mucosa	(45)	(48)	(42)
Inflammation, chronic		1 (2%)	
Fibrosis, focal			1 (2%)
#Ileal mucosa	(45)	(48)	(42)
Inflammation, chronic focal			1 (2%)
Calcification, NOS	2 (4%)		
#Colon	(47)	(47)	(42)
Parasitism	5 (11%)	2 (4%)	2 (5%)
#Colonic mucosa	(47)	(47)	(42)
Calcification, NOS	2 (4%)		
#Cecum	(47)	(47)	(42)
Calcification, NOS	1 (2%)	3 (6%)	
*Rectum	(50)	(50)	(50)
Parasitism	2 (4%)	2 (4%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Hydronephrosis	1 (2%)		
Pyelonephritis, focal	2 (4%)	4 (8%)	1 (2%)
Nephropathy	36 (72%)	43 (86%)	40 (82%)
Calcification, focal	1 (2%)		1 (2%)
Hyperplasia, tubular cell		1 (2%)	
#Kidney/cortex	(50)	(50)	(49)
Cyst, NOS		2 (4%)	
Abscess, NOS			1 (2%)
Inflammation, chronic focal		1 (2%)	
Hyperplasia, tubular cell		8 (16%)	9 (18%)
#Renal papilla	(50)	(50)	(49)
Congestion, NOS		1 (2%)	
Degeneration, NOS		1 (2%)	
Necrosis, NOS	1 (2%)		
Calcification, NOS	12 (24%)	41 (82%)	36 (73%)
#Kidney/tubule	(50)	(50)	(49)
Pigmentation, NOS	3 (6%)	1 (2%)	
#Kidney/pelvis	(50)	(50)	(49)
Calcification, focal	3 (6%)		3 (6%)
Hyperplasia, epithelial		23 (46%)	21 (43%)
#Urinary bladder	(46)	(43)	(41)
Hemorrhage		1 (2%)	
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, chronic focal			1 (2%)
Granuloma, NOS		1 (2%)	
ENDOCRINE SYSTEM			
#Pituitary	(50)	(50)	(46)
Hemorrhage	1 (2%)	1 (2%)	
#Pituitary intermedia	(50)	(50)	(46)
Cyst, NOS		1 (2%)	
#Anterior pituitary	(50)	(50)	(46)
Cyst, NOS	2 (4%)	5 (10%)	3 (7%)
Hyperplasia, focal	16 (32%)	14 (28%)	16 (35%)
Angiectasis	1 (2%)	1 (2%)	4 (9%)
#Pituitary posterior	(50)	(50)	(46)
Metaplasia, osseous		1 (2%)	
#Adrenal	(50)	(50)	(49)
Necrosis, NOS		1 (2%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal cortex	(50)	(50)	(49)
Degeneration, lipoid	9 (18%)	6 (12%)	8 (16%)
Lipoidosis	2 (4%)	1 (2%)	
Cytoplasmic vacuolization	1 (2%)		
Hyperplasia, focal	9 (18%)	2 (4%)	4 (8%)
#Adrenal medulla	(50)	(50)	(49)
Fibrosis, focal		1 (2%)	
Hyperplasia, focal	12 (24%)	8 (16%)	10 (20%)
Angiectasis		1 (2%)	
#Thyroid	(49)	(50)	(49)
Ultimobranchial cyst	1 (2%)		
Hyperplasia, C-cell	6 (12%)	6 (12%)	3 (6%)
Hyperplasia, follicular cell		1 (2%)	
#Parathyroid	(39)	(37)	(42)
Hyperplasia, focal			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Dilatation/ducts		1 (2%)	
Galactocele	1 (2%)		
Lactation	10 (20%)	5 (10%)	1 (2%)
*Mammary lobule	(50)	(50)	(50)
Hyperplasia, NOS	1 (2%)	1 (2%)	
*Preputial gland	(50)	(50)	(50)
Dilatation/ducts		1 (2%)	3 (6%)
Abscess, NOS		1 (2%)	
Inflammation, acute/chronic		2 (4%)	
Inflammation, chronic focal		2 (4%)	
Hyperplasia, NOS		1 (2%)	
Hyperplasia, epithelial		1 (2%)	
#Prostate	(47)	(49)	(47)
Inflammation, suppurative	1 (2%)		
Abscess, NOS			1 (2%)
Inflammation, chronic			2 (4%)
Inflammation, chronic focal	4 (9%)	1 (2%)	2 (4%)
Necrosis, focal		1 (2%)	
Hyperplasia, focal	12 (26%)	9 (18%)	9 (19%)
#Testis	(50)	(50)	(49)
Atrophy, NOS		2 (4%)	2 (4%)
Hyperplasia, interstitial cell	5 (10%)	3 (6%)	3 (6%)
#Spermatid	(50)	(50)	(49)
Cytomegaly	1 (2%)		
*Epididymis	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
Inflammation, chronic focal	1 (2%)		
Fibrosis, focal			1 (2%)
Atrophy, NOS		1 (2%)	
Hyperplasia, mesothelial			1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Hemorrhage	2 (4%)		
Infarct, NOS	1 (2%)		
#Cerebral cortex	(50)	(50)	(50)
Hemorrhage	1 (2%)		
#Medulla oblongata	(50)	(50)	(50)
Demyelinization			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Cataract	4 (8%)		2 (4%)
*Eye/sclera	(50)	(50)	(50)
Metaplasia, osseous	3 (6%)	4 (8%)	5 (10%)
*Eye/retina	(50)	(50)	(50)
Atrophy, NOS	4 (8%)	1 (2%)	4 (8%)
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, suppurative			2 (4%)
Inflammation, chronic	1 (2%)	1 (2%)	8 (16%)
*Ear canal	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Sternum	(50)	(50)	(50)
Traumatic abnormality	1 (2%)		
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
Abscess, NOS		1 (2%)	
*Abdominal cavity	(50)	(50)	(50)
Necrosis, fat		1 (2%)	3 (6%)
*Mesentery	(50)	(50)	(50)
Necrosis, NOS		1 (2%)	
Necrosis, fat	1 (2%)	1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Congestion, NOS	1 (2%)		
Periorbital region			
Hemorrhage	1	2	
Inflammation, suppurative		1	
Adipose tissue			
Necrosis, fat	3	1	
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported			1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

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APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE

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TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	3 (6%)	3 (6%)	2 (4%)
Fibrosarcoma			1 (2%)
Myxosarcoma		1 (2%)	
Rhabdomyosarcoma			1 (2%)
Osteosarcoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(49)
Squamous cell carcinoma, metastatic			1 (2%)
Alveolar/bronchiolar adenoma	1 (2%)		1 (2%)
Alveolar/bronchiolar carcinoma			1 (2%)
Fibrosarcoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS			1 (2%)
Leukemia, mononuclear cell	10 (20%)	9 (18%)	12 (24%)
#Spleen	(50)	(50)	(49)
Leukemia, mononuclear cell			1 (2%)
#Mandibular lymph node	(50)	(50)	(46)
Squamous cell carcinoma, metastatic			1 (2%)
#Thymus	(44)	(49)	(46)
Malignant lymphoma, lymphocytic type		1 (2%)	
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
*Mouth	(50)	(50)	(50)
Squamous cell carcinoma			1 (2%)
*Palate	(50)	(50)	(50)
Squamous cell papilloma			2 (4%)
*Tongue	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		
Squamous cell carcinoma			1 (2%)
#Salivary gland	(50)	(50)	(49)
Adenocarcinoma, NOS		1 (2%)	
Fibrosarcoma		1 (2%)	
#Liver	(50)	(50)	(49)
Neoplastic nodule		2 (4%)	
#Jejunum	(45)	(50)	(47)
Adenomatous polyp, NOS		1 (2%)	
*Rectum	(50)	(50)	(50)
Endometrial stromal sarcoma, invasive		1 (2%)	
URINARY SYSTEM			
#Urinary bladder	(42)	(45)	(44)
Endometrial stromal sarcoma, invasive		1 (2%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(50)	(48)
Carcinoma, NOS	1 (2%)	1 (2%)	2 (4%)
Adenoma, NOS	17 (34%)	21 (42%)	10 (21%)
#Adrenal	(50)	(50)	(49)
Cortical adenoma	1 (2%)	1 (2%)	2 (4%)
Cortical carcinoma			1 (2%)
#Adrenal medulla	(50)	(50)	(49)
Pheochromocytoma	5 (10%)	5 (10%)	1 (2%)
Pheochromocytoma, malignant		3 (6%)	
#Thyroid	(49)	(50)	(48)
Follicular cell adenoma	1 (2%)		1 (2%)
Follicular cell carcinoma			1 (2%)
C-cell adenoma	2 (4%)	3 (6%)	1 (2%)
C-cell carcinoma	3 (6%)	4 (8%)	2 (4%)
#Pancreatic islets	(49)	(50)	(49)
Islet cell adenoma	1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS	2 (4%)	2 (4%)	1 (2%)
Adenocarcinoma, NOS	2 (4%)	2 (4%)	
Fibroadenoma	12 (24%)	12 (24%)	10 (20%)
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	1 (2%)	
Adenoma, NOS	4 (8%)	2 (4%)	2 (4%)
*Vagina	(50)	(50)	(50)
Sarcoma, NOS			1 (2%)
#Uterus	(50)	(50)	(49)
Adenocarcinoma, NOS		2 (4%)	
Sarcoma, NOS	1 (2%)		
Leiomyosarcoma		2 (4%)	
Endometrial stromal polyp	5 (10%)	7 (14%)	6 (12%)
Endometrial stromal sarcoma		2 (4%)	1 (2%)
#Cervix uteri	(50)	(50)	(49)
Fibroma	1 (2%)		1 (2%)
#Ovary	(50)	(50)	(49)
Sertoli cell tumor		1 (2%)	
NERVOUS SYSTEM			
#Brain	(50)	(50)	(49)
Carcinoma, NOS, invasive	1 (2%)	1 (2%)	2 (4%)
Granular cell tumor, NOS			1 (2%)
Glioma, NOS		1 (2%)	
Astrocytoma	1 (2%)		
SPECIAL SENSE ORGANS			
*Ear	(50)	(50)	(50)
Fibrosarcoma		1 (2%)	
Neurilemoma	1 (2%)		1 (2%)
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	
Squamous cell carcinoma			1 (2%)
MUSCULOSKELETAL SYSTEM			
None			

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
Head			
Squamous cell papilloma	1		
Lumbar region			
Chordoma			1
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	10	5	13
Moribund sacrifice	10	13	14
Terminal sacrifice	30	32	23
TUMOR SUMMARY			
Total animals with primary tumors**	40	42	40
Total primary tumors	78	93	72
Total animals with benign tumors	34	36	29
Total benign tumors	58	58	42
Total animals with malignant tumors	19	23	26
Total malignant tumors	20	33	29
Total animals with secondary tumors##	1	2	3
Total secondary tumors	1	4	4
Total animals with tumors uncertain--benign or malignant		2	1
Total uncertain tumors		2	1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE: VEHICLE CONTROL

ANIMAL NUMBER	022	027	038	049	068	012	020	021	029	050	019	030	024	041	035	009	016	038	038	014	001	002	003	004	005
WEEKS ON STUDY	048	070	080	084	086	087	092	092	092	092	093	093	095	097	098	100	102	102	102	103	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Osteosarcoma																	X								
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	–	+	+	+	+	–	+	+	–	+	+	+	+	+	–	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																		X							
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	–	+	+	+	+	+	+	+	–	–	–	+	+	+	–	+	+	+	+	+	+
Large intestine	+	+	+	+	–	+	+	+	+	+	+	–	–	–	–	+	+	+	–	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	–	+	–	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	–	+	–	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS					X																				
Adenoma, NOS							X	X	X		X					X		X						X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																							X		
Pheochromocytoma																						X	X		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																					X				
C-cell adenoma																									X
C cell carcinoma							X															X			
Parathyroid	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS					X																				
Adenocarcinoma, NOS																									
Fibroadenoma							X										X				X			X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																							X		
Adenoma, NOS															X		X			X		X			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS													X												
Fibroma																					X				
Endometrial stromal polyp																									X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive					X																				
Astrocytoma						X																			
SPECIAL SENSE ORGANS																									
Ear	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Neurilemoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell				X						X	X									X	X				
Head, NOS																									
Squamous cell papilloma																		X							

+: Tissue examined microscopically
–: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
.: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

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TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0 0 6	0 0 7	0 1 0	0 1 1	0 1 3	0 1 5	0 1 7	0 1 8	0 2 3	0 2 5	0 2 6	0 3 1	0 3 2	0 3 3	0 3 4	0 3 7	0 3 9	0 4 0	0 4 2	0 4 3	0 4 4	0 4 5	0 4 6	0 4 7	0 4 8	TOTAL:
WEEKS ON STUDY	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma					X								X		X											3
Osteosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Trachea	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	44
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	42
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																										1
Adenoma, NOS						X	X							X		X	X			X	X	X	X			17
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																X										1
Pheochromocytoma													X			X						X				5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																										1
C-cell adenoma																						X				2
C-cell carcinoma															X											3
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	48
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma													X													1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS														X												2
Adenocarcinoma, NOS																		X		X						2
Fibroadenoma				X		X	X					X				X	X					X			X	12
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Adenoma, NOS																										4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																										1
Fibroma																										1
Endometrial stromal polyp	X					X				X														X		5
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										1
Astrocytoma																										1
SPECIAL SENSE ORGANS																										
Ear	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Neurilemoma				X																						1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X					X									X	X		X								10
Head, NOS																										
Squamous cell papilloma																										1

* Animals necropsied

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TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE: LOW DOSE

ANIMAL NUMBER	044	024	038	039	032	002	037	011	021	030	019	043	013	022	050	033	036	051	003	004	005	006	007	008	009
WEEKS ON STUDY	053	038	038	060	085	070	091	092	093	095	096	097	098	098	098	102	102	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																			X						
Mycosarcoma										X															
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, lymphocytic type																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS													X												
Fibrosarcoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																			X						X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																									
Large intestine	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rectum	N	N	N	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
Endometrial stromal sarcoma, invasive											X														
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	–	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+
Endometrial stromal sarcoma, invasive											X														
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS					X	X			X		X	X		X				X		X	X				X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																						X			
Pheochromocytoma								X																	
Pheochromocytoma, malignant												X													
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma							X																		
C-cell carcinoma																									
Parathyroid	–	–	–	–	+	+	+	+	–	–	+	+	–	–	+	+	+	+	+	+	+	–	–	+	
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS														X				X		X					
Fibroadenoma																									
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Leiomyosarcoma					X								X												
Endometrial stromal polyp							X												X	X					
Endometrial stromal sarcoma											X														
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sertoli cell tumor													X												
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																									
Glioma, NOS	X																								
SPECIAL SENSE ORGANS																									
Ear	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell							X	X						X	X		X								

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TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	0110	0112	0114	0115	0116	0117	0118	0120	0123	0125	0126	0127	0128	0129	0131	0134	0135	0140	0141	0142	0145	0146	0147	0148	0149	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma				X																	X					3
Myxosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic																		X								1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, lymphocytic type																									X	1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																										1
Fibrosarcoma																		X								1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenomatous polyp, NOS									X																	1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Rectum	+	+	+	+	+	+	N	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	*50
Endometrial stromal sarcoma, invasive																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	45
Endometrial stromal sarcoma, invasive																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																		X								1
Adenoma, NOS	X				X	X				X		X	X		X	X	X				X	X		X		21
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Pheochromocytoma							X		X	X								X								5
Pheochromocytoma, malignant										X	X															3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma					X											X										3
C-cell carcinoma									X	X	X													X		4
Parathyroid	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	37
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS													X								X					2
Adenocarcinoma, NOS						X										X										2
Fibroadenoma	X	X		X		X											X	X	X	X		X			X	12
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS									X																	1
Adenoma, NOS																			X				X			2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS				X							X															2
Leiomyosarcoma																										2
Endometrial stromal polyp	X																			X	X		X			7
Endometrial stromal sarcoma																X										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sertoli cell tumor																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																		X								1
Glioma, NOS																										1
SPECIAL SENSE ORGANS																										
Ear	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	+	N	N	N	N	N	N	*50
Fibrosarcoma																		X								1
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	+	N	N	N	N	N	N	*50
Carcinoma, NOS																			X							1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X									X									X				X			9

* Animals necropsied

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TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE: HIGH DOSE

ANIMAL NUMBER	0117	0146	0107	0148	0129	0192	0137	0125	0128	0113	0132	0111	0135	0118	0130	0134	0147	0123	0150	0110	0131	0133	0141	0119
WEEKS ON STUDY	0358	0552	0553	0555	0557	0559	0609	0604	0687	0721	0733	0736	0737	0771	0771	0771	0798	0799	0800	0804	0804	0804	0825	0907
INTEGUMENTARY SYSTEM																								
Subcutaneous tissue	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																								
Fibrosarcoma																								
Rhabdomyosarcoma															X									
RESPIRATORY SYSTEM																								
Lungs and bronchi	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																			X					
Alveolar/bronchiolar adenoma																								
Alveolar/bronchiolar carcinoma																								
Trachea	+	+	–	+	+	+	A	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																								
Lymph nodes	+	–	+	+	+	+	A	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																			X					
Thymus	+	+	+	–	+	+	A	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
CIRCULATORY SYSTEM																								
Heart	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma														X										
Squamous cell carcinoma																			X					
Salivary gland	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	–	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	–	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
Kidney	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	A	+	+	–	+	+	+	+	–	+	–	+	–	+	+	–	+	+
ENDOCRINE SYSTEM																								
Pituitary	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Carcinoma, NOS																							X	
Adenoma, NOS														X		X						X		
Adrenal	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																								
Cortical carcinoma																								
Pheochromocytoma																								
Thyroid	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma										X														
Follicular cell carcinoma																					X			
C-cell adenoma																								
C-cell carcinoma																								
Parathyroid	+	–	+	–	–	+	A	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+
Pancreatic islets	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																								
REPRODUCTIVE SYSTEM																								
Mammary gland	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
Adenoma, NOS												X		X	X									
Fibroadenoma																								
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																							X	
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS										X														
Uterus	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																								
Endometrial stromal polyp						X			X		X		X						X					
Endometrial stromal sarcoma																	X							
Ovary	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																								
Brain	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																							X	
Granular cell tumor, NOS																								
SPECIAL SENSE ORGANS																								
Ear	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+
Neurilemoma																								X
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+
Squamous cell carcinoma																								X
ALL OTHER SYSTEMS																								
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS																								
Leukemia, mononuclear cell													X						X		X		X	
Lumbar region																								
Chordoma																								

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TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	024	026	033	034	035	036	038	039	012	015	016	021	022	028	027	034	038	039	040	041	042	043	044	045	049	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	097	102	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma		X		X																						2
Fibrosarcoma				X																						1
Rhabdomyosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma							X																			1
Alveolar/bronchiolar carcinoma																									X	1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia, mononuclear cell																									X	1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Squamous cell carcinoma, metastatic																										1
Thymus	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																			X							2
Squamous cell carcinoma			X																							2
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS														X												2
Adenoma, NOS	X		X					X				X			X					X	X				10
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma					X																	X				2
Cortical carcinoma	X																									1
Pheochromocytoma																				X						1
Thyroid	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma																										1
Follicular cell carcinoma																										1
C-cell adenoma			X																							1
C-cell carcinoma							X				X															2
Parathyroid	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	40
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma	X																									1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																X										1
Fibroadenoma						X		X						X	X	X				X			X			10
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS							X																			2
Vagina	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroma								X																		1
Endometrial stromal polyp			X																							6
Endometrial stromal sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS, invasive														X												2
Granular cell tumor, NOS							X																			1
SPECIAL SENSE ORGANS																										
Ear	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Neurilemoma						X																				1
Zymbal gland	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS										X																1
Leukemia, mononuclear cell		X					X	X	X									X		X		X	X			12
Lumbar region																										
Chordoma	X																									1

* Animals necropsied

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TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE

	Vehicle Control	500 mg/kg	1,000 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	(b) 2/50 (4%)
Adjusted Rates (c)	10.0%	9.1%	8.3%
Terminal Rates (d)	3/30 (10%)	3/33 (9%)	1/23 (4%)
Week of First Observation	105	105	102
Life Table Tests (e)	P=0.533N	P=0.620N	P=0.627N
Incidental Tumor Tests (e)	P=0.573N	P=0.620N	P=0.672
Cochran-Armitage Trend Test (e)	P=0.412N		
Fisher Exact Test (e)		P=0.661	P=0.500N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	10/50 (20%)	9/50 (18%)	13/50 (26%)
Adjusted Rates (c)	27.8%	22.8%	45.0%
Terminal Rates (d)	6/30 (20%)	4/33 (12%)	8/23 (35%)
Week of First Observation	84	91	76
Life Table Tests (e)	P=0.083	P=0.448N	P=0.098
Incidental Tumor Tests (e)	P=0.090	P=0.480	P=0.125
Cochran-Armitage Trend Test (e)	P=0.271		
Fisher Exact Test (e)		P=0.500N	P=0.317
Oral Cavity: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	1/50 (2%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (c)	2.9%	0.0%	13.9%
Terminal Rates (d)	0/30 (0%)	0/33 (0%)	2/23 (9%)
Week of First Observation	102		77
Life Table Tests (e)	P=0.045	P=0.494N	P=0.104
Incidental Tumor Tests (e)	P=0.083	P=0.521N	P=0.163
Cochran-Armitage Trend Test (e)	P=0.082		
Fisher Exact Test (e)		P=0.500N	P=0.181
Pituitary Gland: Adenoma			
Overall Rates (a)	17/50 (34%)	21/50 (42%)	10/48 (21%)
Adjusted Rates (c)	45.7%	52.9%	35.1%
Terminal Rates (d)	11/30 (37%)	15/33 (45%)	6/23 (26%)
Week of First Observation	92	65	77
Life Table Tests (e)	P=0.334N	P=0.372	P=0.354N
Incidental Tumor Tests (e)	P=0.257N	P=0.299	P=0.306N
Cochran-Armitage Trend Test (e)	P=0.103N		
Fisher Exact Test (e)		P=0.268	P=0.109N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	18/50 (36%)	22/50 (44%)	12/48 (25%)
Adjusted Rates (c)	46.9%	55.5%	41.2%
Terminal Rates (d)	11/30 (37%)	16/33 (48%)	7/23 (30%)
Week of First Observation	86	65	77
Life Table Tests (e)	P=0.455N	P=0.376	P=0.494N
Incidental Tumor Tests (e)	P=0.362N	P=0.261	P=0.420N
Cochran-Armitage Trend Test (e)	P=0.155N		
Fisher Exact Test (e)		P=0.270	P=0.168N
Adrenal Gland: Cortical Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	3/49 (6%)
Adjusted Rates (c)	3.3%	3.0%	12.2%
Terminal Rates (d)	1/30 (3%)	1/33 (3%)	2/23 (9%)
Week of First Observation	105	105	97
Life Table Tests (e)	P=0.130	P=0.741N	P=0.210
Incidental Tumor Tests (e)	P=0.102	P=0.741N	P=0.152
Cochran-Armitage Trend Test (e)	P=0.196		
Fisher Exact Test (e)		P=0.753	P=0.301

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	5/50 (10%)	5/50 (10%)	1/49 (2%)
Adjusted Rates (c)	16.7%	14.2%	4.3%
Terminal Rates (d)	5/30 (17%)	4/33 (12%)	1/23 (4%)
Week of First Observation	105	92	105
Life Table Tests (e)	P=0.152N	P=0.578N	P=0.169N
Incidental Tumor Tests (e)	P=0.143N	P=0.612	P=0.169N
Cochran-Armitage Trend Test (e)	P=0.094N		
Fisher Exact Test (e)		P=0.630	P=0.107N
Adrenal Gland: Malignant Pheochromocytoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/49 (0%)
Adjusted Rates (c)	0.0%	8.5%	0.0%
Terminal Rates (d)	0/30 (0%)	2/33 (6%)	0/23 (0%)
Week of First Observation		97	
Life Table Tests (e)	P=0.568	P=0.138	(f)
Incidental Tumor Tests (e)	P=0.506	P=0.128	(f)
Cochran-Armitage Trend Test (e)	P=0.634		
Fisher Exact Test (e)		P=0.121	(f)
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	5/50 (10%)	7/50 (14%)	1/49 (2%)
Adjusted Rates (c)	16.7%	19.2%	4.3%
Terminal Rates (d)	5/30 (17%)	5/33 (15%)	1/23 (4%)
Week of First Observation	105	92	105
Life Table Tests (e)	P=0.190N	P=0.438	P=0.169N
Incidental Tumor Tests (e)	P=0.199N	P=0.356	P=0.169N
Cochran-Armitage Trend Test (e)	P=0.112N		
Fisher Exact Test (e)		P=0.380	P=0.107N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	2/49 (4%)	3/50 (6%)	1/48 (2%)
Adjusted Rates (c)	6.7%	8.2%	4.3%
Terminal Rates (d)	2/30 (7%)	2/33 (6%)	1/23 (4%)
Week of First Observation	105	91	105
Life Table Tests (e)	P=0.514N	P=0.535	P=0.593N
Incidental Tumor Tests (e)	P=0.481N	P=0.423	P=0.593N
Cochran-Armitage Trend Test (e)	P=0.407N		
Fisher Exact Test (e)		P=0.510	P=0.508N
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	3/49 (6%)	4/50 (8%)	2/48 (4%)
Adjusted Rates (c)	8.8%	12.1%	8.7%
Terminal Rates (d)	2/30 (7%)	4/33 (12%)	2/23 (9%)
Week of First Observation	92	105	105
Life Table Tests (e)	P=0.555N	P=0.543	P=0.642N
Incidental Tumor Tests (e)	P=0.526N	P=0.450	P=0.596N
Cochran-Armitage Trend Test (e)	P=0.426N		
Fisher Exact Test (e)		P=0.511	P=0.510N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	5/49 (10%)	7/50 (14%)	3/48 (6%)
Adjusted Rates (c)	15.3%	20.0%	13.0%
Terminal Rates (d)	4/30 (13%)	6/33 (18%)	3/23 (13%)
Week of First Observation	92	91	105
Life Table Tests (e)	P=0.482N	P=0.434	P=0.527N
Incidental Tumor Tests (e)	P=0.440N	P=0.290	P=0.489N
Cochran-Armitage Trend Test (e)	P=0.320N		
Fisher Exact Test (e)		P=0.394	P=0.369N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Mammary Gland: Fibroadenoma			
Overall Rates (a)	12/50 (24%)	12/50 (24%)	10/50 (20%)
Adjusted Rates (c)	36.8%	35.1%	35.9%
Terminal Rates (d)	10/30 (33%)	11/33 (33%)	7/23 (30%)
Week of First Observation	92	98	73
Life Table Tests (e)	P=0.459	P=0.497N	P=0.496
Incidental Tumor Tests (e)	P=0.454N	P=0.568N	P=0.413N
Cochran-Armitage Trend Test (e)	P=0.360N		
Fisher Exact Test (e)		P=0.592	P=0.405N
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	14/50 (28%)	14/50 (28%)	11/50 (22%)
Adjusted Rates (c)	41.2%	41.0%	39.9%
Terminal Rates (d)	11/30 (37%)	13/33 (39%)	8/23 (35%)
Week of First Observation	86	98	73
Life Table Tests (e)	P=0.510	P=0.486N	P=0.541
Incidental Tumor Tests (e)	P=0.390N	P=0.578	P=0.346N
Cochran-Armitage Trend Test (e)	P=0.284N		
Fisher Exact Test (e)		P=0.588	P=0.322N
Mammary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	4/50 (8%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (c)	12.0%	12.1%	4.3%
Terminal Rates (d)	3/30 (10%)	4/33 (12%)	1/23 (4%)
Week of First Observation	86	105	105
Life Table Tests (e)	P=0.227N	P=0.601N	P=0.267N
Incidental Tumor Tests (e)	P=0.212N	P=0.610	P=0.249N
Cochran-Armitage Trend Test (e)	P=0.146N		
Fisher Exact Test (e)		P=0.643	P=0.181N
Clitoral Gland: Adenoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (c)	11.7%	6.1%	7.9%
Terminal Rates (d)	1/30 (3%)	2/33 (6%)	1/23 (4%)
Week of First Observation	98	105	89
Life Table Tests (e)	P=0.373N	P=0.308N	P=0.504N
Incidental Tumor Tests (e)	P=0.459N	P=0.338N	P=0.657N
Cochran-Armitage Trend Test (e)	P=0.252N		
Fisher Exact Test (e)		P=0.339N	P=0.339N
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (c)	14.8%	9.1%	7.9%
Terminal Rates (d)	2/30 (7%)	3/33 (9%)	1/23 (4%)
Week of First Observation	98	105	89
Life Table Tests (e)	P=0.262N	P=0.318N	P=0.372N
Incidental Tumor Tests (e)	P=0.328N	P=0.345N	P=0.502N
Cochran-Armitage Trend Test (e)	P=0.158N		
Fisher Exact Test (e)		P=0.357N	P=0.218N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	5/50 (10%)	7/50 (14%)	6/49 (12%)
Adjusted Rates (c)	16.7%	20.0%	16.0%
Terminal Rates (d)	5/30 (17%)	6/33 (18%)	1/23 (4%)
Week of First Observation	105	91	57
Life Table Tests (e)	P=0.268	P=0.441	P=0.340
Incidental Tumor Tests (e)	P=0.510N	P=0.366	P=0.406N
Cochran-Armitage Trend Test (e)	P=0.424		
Fisher Exact Test (e)		P=0.380	P=0.486

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Uterus: Endometrial Stromal Polyp or Sarcoma			
Overall Rates (a)	5/50 (10%)	9/50 (18%)	7/49 (14%)
Adjusted Rates (c)	16.7%	24.9%	18.5%
Terminal Rates (d)	5/30 (17%)	7/33 (21%)	1/23 (4%)
Week of First Observation	105	91	57
Life Table Tests (e)	P=0.171	P=0.244	P=0.229
Incidental Tumor Tests (e)	P=0.442	P=0.182	P=0.551N
Cochran-Armitage Trend Test (e)	P=0.318		
Fisher Exact Test (e)		P=0.194	P=0.365

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) A fibrosarcoma was also observed in an animal bearing a fibroma.
(c) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(d) Observed tumor incidence at terminal kill
(e) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(f) No P value is reported because no tumors were observed in the 1,000 mg/kg and vehicle control groups.

TABLE B4. HISTORICAL INCIDENCE OF ORAL CAVITY TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	No. of Animals Examined	No. of Tumors in Vehicle Controls	Site	Diagnosis
Historical Incidence at Litton Bionetics, Inc.				
No tumors observed in 450 animals				
Overall Historical Incidence				
	1,450	3	Tongue	Squamous cell papilloma
		1	Tongue (dorsum)	Squamous cell papilloma
		1	Palate	Squamous cell papilloma
TOTAL		5 (0.3%)		

(a) Data as of August 30, 1985, for studies of at least 104 weeks

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)	3 (6%)	3 (6%)
Inflammation, chronic focal			1 (2%)
Reaction, foreign body	3 (6%)		
#Trachea	(49)	(50)	(47)
Inflammation, chronic focal			1 (2%)
#Lung/bronchus	(50)	(50)	(49)
Lymphocytic inflammatory infiltrate			1 (2%)
#Lung	(50)	(50)	(49)
Atelectasis		1 (2%)	
Congestion, NOS	1 (2%)	3 (6%)	2 (4%)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)		1 (2%)
Inflammation, interstitial	1 (2%)	1 (2%)	
Pneumonia, interstitial chronic	1 (2%)	1 (2%)	
Inflammation, chronic focal	3 (6%)	4 (8%)	1 (2%)
Inflammation, granulomatous focal			1 (2%)
Reaction, foreign body	1 (2%)		
Calcification, focal			2 (4%)
Hyperplasia, alveolar epithelium	1 (2%)		1 (2%)
#Lung/alveoli	(50)	(50)	(49)
Histiocytosis	16 (32%)	19 (38%)	18 (37%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(50)	(48)
Inflammation, granulomatous focal			2 (4%)
Fibrosis, focal			1 (2%)
Hypoplasia, NOS	2 (4%)		
Atrophy, focal		1 (2%)	
Hyperplasia, granulocytic		1 (2%)	
#Spleen	(50)	(50)	(49)
Congestion, NOS			1 (2%)
Granuloma, NOS		1 (2%)	
Hemosiderosis	6 (12%)		5 (10%)
Metaplasia, osseous		1 (2%)	
Hematopoiesis	4 (8%)	2 (4%)	3 (6%)
#Splenic capsule	(50)	(50)	(49)
Hyperplasia, focal	1 (2%)		
#Lymph node	(50)	(50)	(46)
Plasmacytosis		1 (2%)	
#Lung/bronchus	(50)	(50)	(49)
Hyperplasia, lymphoid			1 (2%)
#Ileum	(45)	(50)	(47)
Hyperplasia, lymphoid	1 (2%)		
#Colon	(44)	(49)	(47)
Hyperplasia, lymphoid		1 (2%)	

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Thymus	(44)	(49)	(46)
Cyst, NOS		3 (6%)	1 (2%)
Hemorrhage			2 (4%)
Atrophy, NOS	1 (2%)		
Hyperplasia, epithelial	2 (5%)		1 (2%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Periarteritis	1 (2%)		1 (2%)
#Mediastinal lymph node	(50)	(50)	(46)
Lymphangiectasis			1 (2%)
#Myocardium	(50)	(50)	(49)
Fibrosis, focal			1 (2%)
Degeneration, NOS	30 (60%)	31 (62%)	27 (55%)
#Endocardium	(50)	(50)	(49)
Inflammation, chronic		1 (2%)	
*Blood vessel	(50)	(50)	(50)
Aneurysm	1 (2%)		
Inflammation, chronic	1 (2%)		
*Pulmonary artery	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
Calcification, focal	9 (18%)	11 (22%)	8 (16%)
#Kidney	(50)	(50)	(49)
Periarteritis	1 (2%)		
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Hyperplasia, epithelial			1 (2%)
*Tooth	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
#Parotid duct	(50)	(50)	(49)
Necrosis, NOS	1 (2%)		
#Major sublingual duct	(50)	(50)	(49)
Hyperplasia, epithelial	1 (2%)		
#Liver	(50)	(50)	(49)
Congenital malformation, NOS	3 (6%)	1 (2%)	1 (2%)
Hernia, NOS	5 (10%)	1 (2%)	4 (8%)
Deformity, NOS		1 (2%)	
Bile stasis			1 (2%)
Congestion, NOS		1 (2%)	
Hemorrhage		1 (2%)	1 (2%)
Inflammation, acute necrotizing			1 (2%)
Inflammation, chronic focal	16 (32%)	18 (36%)	17 (35%)
Inflammation, granulomatous			1 (2%)
Inflammation, granulomatous focal		1 (2%)	
Necrosis, focal	1 (2%)	2 (4%)	1 (2%)
Lipoidosis	1 (2%)	2 (4%)	1 (2%)
Basophilic cyto change	17 (34%)	7 (14%)	5 (10%)
Ground glass cyto change	3 (6%)	5 (10%)	5 (10%)
Focal cellular change	1 (2%)	1 (2%)	1 (2%)
Eosinophilic cyto change	1 (2%)	1 (2%)	
Clear cell change	3 (6%)	1 (2%)	1 (2%)
Hyperplasia, nodular		1 (2%)	
Angiectasis		2 (4%)	
Regeneration, NOS	3 (6%)	3 (6%)	
#Liver/centrilobular	(50)	(50)	(49)
Degeneration, NOS		1 (2%)	
Necrosis, NOS	1 (2%)		
Lipoidosis	1 (2%)	1 (2%)	

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Liver/periportal	(50)	(50)	(49)
Inflammation, chronic			2 (4%)
Metamorphosis, fatty		1 (2%)	
Lipoidosis	2 (4%)	1 (2%)	2 (4%)
#Liver/hepatocytes	(50)	(50)	(49)
Hyperplasia, diffuse		1 (2%)	
#Bile duct	(50)	(50)	(49)
Cyst		1 (2%)	
Hyperplasia, NOS	30 (60%)	29 (58%)	28 (57%)
#Pancreas	(49)	(50)	(49)
Dilatation/ducts			1 (2%)
Inflammation, chronic focal			1 (2%)
Atrophy, NOS	1 (2%)		
#Pancreatic acinus	(49)	(50)	(49)
Atrophy, NOS	2 (4%)	2 (4%)	1 (2%)
Atrophy, focal	8 (16%)	10 (20%)	8 (16%)
Hyperplasia, focal		1 (2%)	
#Periesophageal tissue	(50)	(50)	(49)
Hemorrhage		1 (2%)	
#Glandular stomach	(48)	(50)	(49)
Dilatation, NOS	1 (2%)		
Inflammation, serous		1 (2%)	
#Forestomach	(48)	(50)	(49)
Ulcer, NOS	1 (2%)		
Inflammation, acute	1 (2%)		
Inflammation, chronic focal		1 (2%)	
Hyperplasia, epithelial	2 (4%)	1 (2%)	
#Duodenum	(45)	(50)	(47)
Ulcer, NOS	1 (2%)		
Inflammation, chronic		1 (2%)	
#Colon	(44)	(49)	(47)
Parasitism	1 (2%)	2 (4%)	1 (2%)
#Colonic mucosa	(44)	(49)	(47)
Calcification, NOS		1 (2%)	1 (2%)
#Cecum	(44)	(49)	(47)
Parasitism			1 (2%)
Calcification, NOS		1 (2%)	3 (6%)
*Rectum	(50)	(50)	(50)
Parasitism	2 (4%)	3 (6%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Nephropathy	9 (18%)	17 (34%)	14 (29%)
Calcification, focal	2 (4%)	3 (6%)	1 (2%)
#Kidney/cortex	(50)	(50)	(49)
Cyst, NOS		1 (2%)	
Fibrosis, focal		1 (2%)	
#Renal papilla	(50)	(50)	(49)
Calcification, NOS	22 (44%)	12 (24%)	7 (14%)
#Kidney/pelvis	(50)	(50)	(49)
Dilatation, NOS			1 (2%)
Calcification, focal	22 (44%)	27 (54%)	13 (27%)
Hyperplasia, epithelial		1 (2%)	2 (4%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(50)	(48)
Hemorrhage			1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Anterior pituitary	(50)	(50)	(48)
Cyst, NOS	13 (26%)	17 (34%)	19 (40%)
Hemorrhage	3 (6%)		
Hyperplasia, focal	16 (32%)	13 (26%)	12 (25%)
Angiectasis	6 (12%)	5 (10%)	6 (13%)
#Pituitary posterior	(50)	(50)	(48)
Gliosis	1 (2%)		
Pigmentation, NOS	1 (2%)		
Metaplasia, osseous		1 (2%)	
#Adrenal cortex	(50)	(50)	(49)
Cyst, NOS	2 (4%)		
Degeneration, lipoid	12 (24%)	11 (22%)	10 (20%)
Necrosis, NOS		1 (2%)	
Necrosis, focal	1 (2%)	1 (2%)	
Lipoidosis	2 (4%)	2 (4%)	
Cytomegaly			1 (2%)
Hyperplasia, focal	8 (16%)	8 (16%)	7 (14%)
#Adrenal medulla	(50)	(50)	(49)
Hyperplasia, focal	5 (10%)	5 (10%)	4 (8%)
#Thyroid	(49)	(50)	(48)
Ultimobranchial cyst		1 (2%)	
Hyperplasia, cystic			1 (2%)
Hyperplasia, C-cell	14 (29%)	10 (20%)	7 (15%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Galactocele	2 (4%)		
Inflammation, chronic			1 (2%)
Lactation	37 (74%)	35 (70%)	26 (52%)
*Mammary duct	(50)	(50)	(50)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal			1 (2%)
*Mammary lobule	(50)	(50)	(50)
Hyperplasia, NOS	1 (2%)		1 (2%)
*Clitoral gland	(50)	(50)	(50)
Dilatation/ducts	1 (2%)	2 (4%)	2 (4%)
Retention of content	2 (4%)	1 (2%)	2 (4%)
Inflammation, acute	2 (4%)		
Inflammation, acute/chronic	1 (2%)		
Hyperplasia, NOS	1 (2%)		
#Uterus	(50)	(50)	(49)
Abscess, NOS		1 (2%)	
Decidual alteration, NOS			1 (2%)
#Cervix uteri	(50)	(50)	(49)
Abscess, NOS		1 (2%)	
Hyperplasia, epithelial	1 (2%)		
#Uterus/endometrium	(50)	(50)	(49)
Cyst, NOS	2 (4%)	1 (2%)	1 (2%)
Inflammation, suppurative			1 (2%)
Hyperplasia, cystic	2 (4%)	3 (6%)	2 (4%)
Hyperplasia, stromal	1 (2%)	1 (2%)	
#Endometrial gland	(50)	(50)	(49)
Cyst, NOS	1 (2%)		
Hyperplasia, NOS	1 (2%)		
#Ovary	(50)	(50)	(49)
Cyst, NOS	2 (4%)	3 (6%)	2 (4%)
Corpus luteum cyst	1 (2%)		
Atrophy, NOS			1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
NERVOUS SYSTEM			
#Lateral ventricle	(50)	(50)	(49)
Dilatation, NOS			1 (2%)
#Aqueduct of Sylvius	(50)	(50)	(49)
Dilatation, NOS		1 (2%)	
*Choroid plexus	(50)	(50)	(50)
Hyperplasia, NOS		1 (2%)	
#Brain	(50)	(50)	(49)
Scar		1 (2%)	
Infarct, hemorrhagic	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Cataract	7 (14%)	7 (14%)	3 (6%)
*Eye/sclera	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
Metaplasia, osseous	1 (2%)	3 (6%)	2 (4%)
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS	1 (2%)		
Atrophy, NOS	5 (10%)	9 (18%)	5 (10%)
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
Inflammation, chronic			2 (4%)
MUSCULOSKELETAL SYSTEM			
*Cartilage, NOS	(50)	(50)	(50)
Necrosis, NOS	1 (2%)		
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, suppurative	1 (2%)		
Inflammation, fibrinous		1 (2%)	
Abscess, NOS			1 (2%)
Hemosiderosis		1 (2%)	
*Pericardium	(50)	(50)	(50)
Inflammation, fibrinous		1 (2%)	
*Mesentery	(50)	(50)	(50)
Necrosis, fat		1 (2%)	1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Congestion, NOS			1 (2%)
Adipose tissue			
Necrosis, NOS		1	
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported			1
Auto/necropsy/no histocytic			1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

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APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE

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TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	47
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)	3 (6%)	
Fibroma	2 (4%)	1 (2%)	
Fibrosarcoma	4 (8%)	3 (6%)	
Rhabdomyosarcoma	2 (4%)		1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(45)
Squamous cell carcinoma	1 (2%)		
Bile duct carcinoma, metastatic		1 (2%)	
Hepatocellular carcinoma, metastatic	2 (4%)		1 (2%)
Alveolar/bronchiolar adenoma	4 (8%)		2 (4%)
Alveolar/bronchiolar carcinoma	2 (4%)		1 (2%)
Carcinosarcoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, lymphocytic type	1 (2%)	1 (2%)	1 (2%)
Malignant lymphoma, mixed type	1 (2%)	2 (4%)	
Granulocytic leukemia	1 (2%)		
#Lymph node	(46)	(43)	(27)
Squamous cell carcinoma, metastatic	1 (2%)		
Fibrosarcoma, metastatic	1 (2%)	1 (2%)	
#Hepatic lymph node	(46)	(43)	(27)
Carcinosarcoma, metastatic	1 (2%)		
#Inguinal lymph node	(46)	(43)	(27)
Fibrosarcoma, metastatic	1 (2%)		
#Thymus	(38)	(41)	(41)
Bile duct carcinoma, metastatic		1 (2%)	
Carcinosarcoma, metastatic	1 (3%)		
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)	
#Spleen	(50)	(49)	(46)
Hemangiosarcoma	2 (4%)		
#Heart	(50)	(49)	(45)
Bile duct carcinoma, metastatic		1 (2%)	
Sarcoma, NOS	1 (2%)		
#Liver	(50)	(50)	(46)
Hemangiosarcoma	3 (6%)		1 (2%)
#Pancreas	(49)	(49)	(46)
Hemangioma	1 (2%)		
#Urinary bladder	(46)	(45)	(38)
Hemangioma	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(46)
Bile duct carcinoma		1 (2%)	
Hepatocellular adenoma	12 (24%)	15 (30%)	3 (7%)
Hepatocellular carcinoma	6 (12%)	6 (12%)	1 (2%)
Carcinosarcoma, metastatic	1 (2%)		

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Pancreas	(49)	(49)	(46)
Bile duct carcinoma, metastatic		1 (2%)	
Carcinosarcoma	1 (2%)		
#Forestomach	(46)	(48)	(43)
Papilloma, NOS	1 (2%)		
Squamous cell carcinoma	1 (2%)		
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Adrenal/capsule	(50)	(49)	(44)
Adenoma, NOS	1 (2%)		
#Adrenal medulla	(50)	(49)	(44)
Pheochromocytoma	4 (8%)		
#Thyroid	(49)	(46)	(43)
Follicular cell adenoma	2 (4%)		
Follicular cell carcinoma	1 (2%)		
REPRODUCTIVE SYSTEM			
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)		
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	2 (4%)		
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Bile duct carcinoma, metastatic		1 (2%)	
ALL OTHER SYSTEMS			
Adipose tissue			
Carcinosarcoma, metastatic	1		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	15	26	25
Moribund sacrifice	3	7	8
Terminal sacrifice	28	12	
Dosing accident	4	5	17

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	34	27	10
Total primary tumors	60	33	10
Total animals with benign tumors	24	16	5
Total benign tumors	30	16	5
Total animals with malignant tumors	23	14	5
Total malignant tumors	30	17	5
Total animals with secondary tumors##	5	2	1
Total secondary tumors	10	6	1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE: VEHICLE CONTROL

| ANIMAL NUMBER | 0 0 0

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0 0 5	0 1 5	0 1 6	0 1 7	0 1 8	0 1 9	0 2 1	0 2 3	0 2 4	0 2 6	0 2 9	0 3 0	0 3 2	0 3 3	0 3 4	0 3 8	0 3 7	0 3 8	0 3 9	0 4 0	0 4 1	0 4 2	0 4 3	0 4 5	0 5 0	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 *	1 0 5	1 0 3	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma											X										X					2
Fibrosarcoma							X					X	X													4
Rhabdomyosarcoma																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma													X													1
Hepatocellular carcinoma, metastatic							X																			2
Alveolar/bronchiolar adenoma		X														X			X							4
Alveolar/bronchiolar carcinoma	X																						X			2
Carcinosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma				X																			X			2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma, metastatic								X																		1
Fibrosarcoma, metastatic																										1
Carcinosarcoma, metastatic																										1
Thymus	+	+	–	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	38
Carcinosarcoma, metastatic																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X			X								X	X	X		X		X					X			12
Hepatocellular carcinoma							X																X			6
Carcinosarcoma, metastatic																										1
Hemangiosarcoma					X				X																	3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinosarcoma																										1
Hemangioma																	X									1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papilloma, NOS			X																							1
Squamous cell carcinoma								X																		1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Large intestine	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangioma															X											1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	43
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS				X																						1
Pheochromocytoma																					X			X		4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma			X																							2
Follicular cell carcinoma																	X									1
Parathyroid	–	–	–	+	+	–	–	+	+	+	+	–	+	–	–	+	–	–	–	–	+	+	+	+	+	20
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS								X																		1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS		X							X																	2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																										1
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type																										1
Granulocytic leukemia													X													1
Adipose tissue																										
Carcinosarcoma, metastatic																										1

* Animals necropsied

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TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE: LOW DOSE

ANIMAL NUMBER	003	002	022	021	023	037	012	032	042	026	004	006	007	008	009	011	013	014	017	045	046	018	041	001	031
WEEKS ON STUDY	001	016	017	018	023	039	055	053	064	072	077	077	077	077	077	077	077	077	077	077	077	081	082	088	090
INTEGUMENTARY SYSTEM	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue									X																
Sarcoma, NOS																									
Fibroma																									
Fibrosarcoma																									
RESPIRATORY SYSTEM	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lungs and bronchi																				X					
Bile duct carcinoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	–	+	–	+	–	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+
Fibrosarcoma, metastatic																									
Thymus	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct carcinoma, metastatic																				X					
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct carcinoma, metastatic																				X					
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct carcinoma																				X					
Hepatocellular adenoma							X			X					X		X		X	X					
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	+	N	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct carcinoma, metastatic																				X					
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	–	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
URINARY SYSTEM	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Kidney	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Urinary bladder																									
ENDOCRINE SYSTEM	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Thyroid	–	–	+	–	–	–	–	+	+	+	+	–	–	+	+	+	–	–	+	+	–	+	+	–	–
Parathyroid																									
REPRODUCTIVE SYSTEM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testis	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Prostate																									
NERVOUS SYSTEM	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Brain																									
BODY CAVITIES	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mediastinum																				X					
Bile duct carcinoma, metastatic																									
ALL OTHER SYSTEMS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Multiple organs, NOS																								X	
Hemangiosarcoma																									X
Malignant lymphoma, lymphocytic type																									
Malignant lymphoma, mixed type																									

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TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	0 0 5	0 3 9	0 2 9	0 3 4	0 3 0	0 3 3	0 1 6	0 1 5	0 3 8	0 4 8	0 1 9	0 3 5	0 2 8	0 1 0	0 2 0	0 2 4	0 2 5	0 2 7	0 3 6	0 4 0	0 4 3	0 4 4	0 4 7	0 4 9	0 5 0	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	0 9 3	0 9 3	0 9 4	0 9 4	0 9 5	0 9 5	0 9 6	0 9 7	0 9 7	0 9 7	0 9 9	0 9 9	1 0 0	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS			X										X													3
Fibroma						X																				1
Fibrosarcoma						X		X											X							3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct carcinoma, metastatic																										1
Trachea	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Fibrosarcoma, metastatic																			X							1
Thymus	+	+	+	−	−	−	+	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	41
Bile duct carcinoma, metastatic																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct carcinoma, metastatic																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct carcinoma																										1
Hepatocellular adenoma		X			X						X	X		X		X	X		X	X			X		X	15
Hepatocellular carcinoma	X					X				X														X		6
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct carcinoma, metastatic																										1
Esophagus	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	−	−	−	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Large intestine	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	−	+	[illegible]			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	−	−	+	[illegible]			+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	45
Adrenal	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Parathyroid	+	−	+	−	−	−	−	+	−	−	−	−	+	−	+	−	−	−	+	−	+	+	+	−		21
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	46
NERVOUS SYSTEM																										
Brain	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Bile duct carcinoma, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																										1
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type																			X					X		2

* Animals necropsied

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TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE: HIGH DOSE

ANIMAL NUMBER	00007	00009	00103	00126	00236	00361	00021	00022	00233	00241	00220	00353	00301	00111	00968	00491	00172	00253	00372	00222	00035	00085	00135
WEEKS ON STUDY	00044	00111	00177	00188	00188	00188	00220	00221	00222	00233	00233	00244	00268	00311	00344	00365	00439	00433	00433	00444	00445	00455	00455
INTEGUMENTARY SYSTEM																							
Subcutaneous tissue	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
Rhabdomyosarcoma																									
RESPIRATORY SYSTEM																							
Lungs and bronchi	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Trachea	A	+	+	–	+	+	+	+	A	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																							
Bone marrow	A	–	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	A	+	+	+	+	+	+	–	A	–	–	+	+	+	–	+	–	+	+	+	+	–	–	+	–
Thymus	A	–	+	+	+	+	+	+	A	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																							
Heart	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																							
Salivary gland	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																									
Hemangiosarcoma																									X
Bile duct	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	+	+	N	+	N	N	N	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+
Pancreas	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	A	+	–	–	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Small intestine	A	+	+	+	+	+	+	+	A	+	–	+	–	+	+	+	–	+	–	+	+	+	–	+	+
Large intestine	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
URINARY SYSTEM																							
Kidney	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+
ENDOCRINE SYSTEM																							
Pituitary	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	A	+	+	+	+	+	+	+	A	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+
Thyroid	A	+	+	–	+	+	+	+	A	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	A	+	–	–	–	+	–	–	A	+	–	+	–	–	+	–	–	–	+	–	+	+	–	+	+
REPRODUCTIVE SYSTEM																							
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	+	N
Testis	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
NERVOUS SYSTEM																							
Brain	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																							
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type																									

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TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE
(Continued)

ANIMAL NUMBER	0114	0118	0119	0124	0128	0129	0131	0132	0133	0134	0139	0142	0148	0150	0153	0143	0146	0116	0140	0115	0104	0127	0144	0145	0147	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	045	045	045	045	045	045	045	045	045	045	045	045	045	045	045	068	070	074	074	077	079	080	092	092	092	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	50
Rhabdomyosarcoma																						X				1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+	+	45
Hepatocellular carcinoma, metastatic																						X				1
Alveolar/bronchiolar adenoma												X													X	2
Alveolar/bronchiolar carcinoma																			X							1
Trachea	+	+	+	+	–	+	+	+	–	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+	+	42
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+	+	46
Lymph nodes	+	+	+	+	–	–	–	–	–	–	–	–	+	+	–	A	+	+	+	+	+	–	+	–	+	27
Thymus	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	A	+	+	+	+	+	–	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+	+	45
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+	+	46
Hepatocellular adenoma																		X		X			X			3
Hepatocellular carcinoma																						X				1
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+	+	46
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	N	+	+	+	+	+	N	N	+	+	+	+	+	N	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+	+	46
Esophagus	–	+	+	+	–	+	+	+	+	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+	+	42
Stomach	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+	+	43
Small intestine	+	–	+	–	+	+	+	+	–	+	+	–	+	+	–	A	+	+	+	+	+	–	–	–	+	34
Large intestine	+	+	+	–	+	+	+	+	–	+	+	+	+	+	–	A	+	+	+	+	+	–	+	–	+	41
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+	+	46
Urinary bladder	+	–	+	–	+	+	+	+	–	+	+	–	+	+	–	A	+	+	+	+	+	+	–	–	+	38
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+	–	43
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+	+	44
Thyroid	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+	+	43
Parathyroid	–	+	–	+	–	–	–	–	–	+	+	–	–	+	–	A	+	–	–	+	–	–	+	+	+	20
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+	+	46
Prostate	+	+	+	+	+	+	+	+	+	–	+	–	+	+	–	A	+	+	+	+	+	+	+	+	+	43
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	47
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, lymphocytic type																								X		1

* Animals necropsied

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TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE

	Vehicle Control	1,000 mg/kg	2,000 mg/kg
Subcutaneous Tissue: Sarcoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	3.3%	13.8%	0.0%
Terminal Rates (c)	0/29 (0%)	0/12 (0%)	0/0
Week of First Observation	104	64	
Life Table Tests (d)	P=0.220	P=0.149	(e)
Incidental Tumor Tests (d)	P=0.569N	P=0.714N	(e)
Cochran-Armitage Trend Test (d)	P=0.378N		
Fisher Exact Test (d)		P=0.309	P=0.500N
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	4/50 (8%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	12.6%	17.5%	0.0%
Terminal Rates (c)	3/29 (10%)	1/12 (8%)	0/0
Week of First Observation	80	95	
Life Table Tests (d)	P=0.481	P=0.452	P=0.919N
Incidental Tumor Tests (d)	P=0.466N	P=0.646N	P=0.500N
Cochran-Armitage Trend Test (d)	P=0.049N		
Fisher Exact Test (d)		P=0.500N	P=0.059N
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	5/50 (10%)	6/50 (12%)	0/50 (0%)
Adjusted Rates (b)	15.6%	28.9%	0.0%
Terminal Rates (c)	3/29 (10%)	1/12 (8%)	0/0
Week of First Observation	80	64	
Life Table Tests (d)	P=0.202	P=0.145	P=0.919N
Incidental Tumor Tests (d)	P=0.388N	P=0.612N	P=0.500N
Cochran-Armitage Trend Test (d)	P=0.042N		
Fisher Exact Test (d)		P=0.500	P=0.028N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	6/50 (12%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	19.4%	17.5%	0.0%
Terminal Rates (c)	5/29 (17%)	1/12 (8%)	0/0
Week of First Observation	80	95	
Life Table Tests (d)	P=0.634N	P=0.628	P=0.919N
Incidental Tumor Tests (d)	P=0.318N	P=0.456N	P=0.500N
Cochran-Armitage Trend Test (d)	P=0.010N		
Fisher Exact Test (d)		P=0.243N	P=0.013N
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	7/50 (14%)	6/50 (12%)	0/50 (0%)
Adjusted Rates (b)	22.1%	28.9%	0.0%
Terminal Rates (c)	5/29 (17%)	1/12 (8%)	0/0
Week of First Observation	80	64	
Life Table Tests (d)	P=0.326	P=0.262	P=0.919N
Incidental Tumor Tests (d)	P=0.270N	P=0.448N	P=0.500N
Cochran-Armitage Trend Test (d)	P=0.010N		
Fisher Exact Test (d)		P=0.500N	P=0.006N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	4/50 (8%)	0/49 (0%)	2/45 (4%)
Adjusted Rates (b)	12.8%	0.0%	35.8%
Terminal Rates (c)	3/29 (10%)	0/12 (0%)	0/0
Week of First Observation	90		45
Life Table Tests (d)	P=0.285	P=0.191N	P=0.060
Incidental Tumor Tests (d)	P=0.523N	P=0.184N	P=0.650
Cochran-Armitage Trend Test (d)	P=0.253N		
Fisher Exact Test (d)		P=0.061N	P=0.390N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	1,000 mg/kg	2,000 mg/kg
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	0/49 (0%)	3/45 (7%)
Adjusted Rates (b)	19.5%	0.0%	43.8%
Terminal Rates (c)	5/29 (17%)	0/12 (0%)	0/0
Week of First Observation	90		45
Life Table Tests (d)	P=0.168	P=0.101N	P=0.006
Incidental Tumor Tests (d)	P=0.592N	P=0.097N	P=0.485
Cochran-Armitage Trend Test (d)	P=0.177N		
Fisher Exact Test (d)		P=0.014N	P=0.299N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	6.6%	19.9%	33.3%
Terminal Rates (c)	1/29 (3%)	2/12 (17%)	0/0
Week of First Observation	102	90	92
Life Table Tests (d)	P=0.026	P=0.182	P=0.059
Incidental Tumor Tests (d)	P=0.268	P=0.327	P=0.500
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test (d)		P=0.500	P=0.500N
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	9.9%	19.9%	33.3%
Terminal Rates (c)	2/29 (7%)	2/12 (17%)	0/0
Week of First Observation	102	90	92
Life Table Tests (d)	P=0.054	P=0.283	P=0.059
Incidental Tumor Tests (d)	P=0.344	P=0.441	P=0.500
Cochran-Armitage Trend Test (d)	P=0.238N		
Fisher Exact Test (d)		P=0.661	P=0.309N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	6/50 (12%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	18.6%	3.7%	3.6%
Terminal Rates (c)	4/29 (14%)	0/12 (0%)	0/0
Week of First Observation	87	88	45
Life Table Tests (d)	P=0.511N	P=0.220N	P=0.478
Incidental Tumor Tests (d)	P=0.125N	P=0.139N	P=0.616N
Cochran-Armitage Trend Test (d)	P=0.023N		
Fisher Exact Test (d)		P=0.056N	P=0.056N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	8/50 (16%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	25.1%	3.7%	3.6%
Terminal Rates (c)	6/29 (21%)	0/12 (0%)	0/0
Week of First Observation	87	88	45
Life Table Tests (d)	P=0.369N	P=0.128N	P=0.478
Incidental Tumor Tests (d)	P=0.078N	P=0.077N	P=0.616N
Cochran-Armitage Trend Test (d)	P=0.005N		
Fisher Exact Test (d)		P=0.016N	P=0.016N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	12/50 (24%)	15/50 (30%)	3/46 (7%)
Adjusted Rates (b)	38.5%	70.1%	51.4%
Terminal Rates (c)	10/29 (34%)	7/12 (58%)	0/0
Week of First Observation	93	55	74
Life Table Tests (d)	P<0.001	P=0.006	P<0.001
Incidental Tumor Tests (d)	P=0.051	P=0.180	P=0.196
Cochran-Armitage Trend Test (d)	P=0.026N		
Fisher Exact Test (d)		P=0.326	P=0.018N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	1,000 mg/kg	2,000 mg/kg
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	6/50 (12%)	6/50 (12%)	1/46 (2%)
Adjusted Rates (b)	16.8%	24.8%	20.0%
Terminal Rates (c)	2/29 (7%)	1/12 (8%)	0/0
Week of First Observation	58	77	79
Life Table Tests (d)	P=0.175	P=0.319	P=0.430
Incidental Tumor Tests (d)	P=0.245N	P=0.215N	P=0.419N
Cochran-Armitage Trend Test (d)	P=0.069N		
Fisher Exact Test (d)		P=0.620N	P=0.070N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	17/50 (34%)	21/50 (42%)	4/46 (9%)
Adjusted Rates (b)	49.4%	80.5%	61.1%
Terminal Rates (c)	12/29 (41%)	8/12 (67%)	0/0
Week of First Observation	58	55	74
Life Table Tests (d)	P<0.001	P=0.003	P<0.001
Incidental Tumor Tests (d)	P=0.156	P=0.341	P=0.500
Cochran-Armitage Trend Test (d)	P=0.005N		
Fisher Exact Test (d)		P=0.268	P=0.003N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	4/50 (8%)	0/49 (0%)	0/44 (0%)
Adjusted Rates (b)	12.7%	0.0%	0.0%
Terminal Rates (c)	3/29 (10%)	0/12 (0%)	0/0
Week of First Observation	85		
Life Table Tests (d)	P=0.185N	P=0.192N	P=0.949N
Incidental Tumor Tests (d)	P=0.114N	P=0.184N	P=0.500N
Cochran-Armitage Trend Test (d)	P=0.018N		
Fisher Exact Test (d)		P=0.061N	P=0.076N
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	3/49 (6%)	0/46 (0%)	0/43 (0%)
Adjusted Rates (b)	9.0%	0.0%	0.0%
Terminal Rates (c)	2/29 (7%)	0/12 (0%)	0/0
Week of First Observation	42		
Life Table Tests (d)	P=0.165N	P=0.235N	P=0.564N
Incidental Tumor Tests (d)	P=0.049N	P=0.298N	P=0.215N
Cochran-Armitage Trend Test (d)	P=0.045N		
Fisher Exact Test (d)		P=0.133N	P=0.147N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because all high dose animals died before the vehicle control tumor was observed.

TABLE C4a. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls	
	Lymphoma	Lymphoma or Leukemia
Historical Incidence at Litton Bionetics, Inc.		
Dimethyl hydrogen phosphite	3/50	5/50
Dimethyl methylphosphonate	2/50	3/50
2,4-Toluene diisocyanate	6/50	6/50
Diallyl phthalate	6/50	6/50
Dimethyl morpholinophosphoramidate	3/50	3/50
Tris(2-ethylhexyl)phosphate	7/50	7/50
3-Chloro-2-methylpropene	4/50	4/50
4-Vinylcyclohexene	4/50	4/50
Dimethylvinyl chloride	6/50	6/50
TOTAL	41/450 (9.1%)	44/450 (9.8%)
SD (b)	3.48%	2.91%
Range (c)		
High	7/50	7/50
Low	2/50	3/50
Overall Historical Incidence		
TOTAL	181/1,497 (12.1%)	185/1,497 (12.4%)
SD (b)	4.41%	4.21%
Range (c)		
High	11/50	11/50
Low	2/50	3/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE C4b. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Litton Bionetics, Inc.			
Dimethyl hydrogen phosphite	12/50	9/50	19/50
Dimethyl methylphosphonate	10/50	6/50	15/50
2,4-Toluene diisocyanate	5/49	6/49	11/49
Diallyl phthalate	0/50	7/50	7/50
Dimethyl morpholinophosphoramidate	6/50	6/50	11/50
Tris(2-ethylhexyl)phosphate	7/50	9/50	15/50
3-Chloro-2-methylpropene	4/50	19/50	22/50
4-Vinylcyclohexene	7/49	11/49	18/49
Dimethylvinyl chloride	8/49	3/49	11/49
TOTAL	59/447 (13.2%)	76/447 (17.0%)	129/447 (28.9%)
SD (b)	6.95%	9.17%	9.54%
Range (c)			
High	12/50	19/50	22/50
Low	0/50	3/49	7/50
Overall Historical Incidence			
TOTAL	201/1,490 (13.5%)	306/1,490 (20.5%)	477/1,490 (32.0%)
SD (b)	6.45%	7.70%	8.99%
Range (c)			
High	14/50	19/50	25/50
Low	0/50	3/49	7/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	47
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst		1 (2%)	
Ulcer, NOS	1 (2%)	5 (10%)	5 (10%)
Inflammation, acute		2 (4%)	
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic	1 (2%)	1 (2%)	2 (4%)
Fibrosis	1 (2%)		
Fibrosis, focal	1 (2%)		
Exfoliative dermatitis	1 (2%)		
Hyperplasia, NOS		1 (2%)	
Acanthosis			2 (4%)
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Congenital malformation, NOS		1 (2%)	
Ectopia	1 (2%)		
#Lung	(50)	(49)	(45)
Bronchiectasis	1 (2%)		
Atelectasis		1 (2%)	2 (4%)
Congestion, NOS	2 (4%)	8 (16%)	16 (36%)
Hemorrhage	2 (4%)	1 (2%)	
Bronchopneumonia, focal			1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)	1 (2%)	
Inflammation, interstitial	1 (2%)	1 (2%)	
Inflammation, chronic	1 (2%)		
Fibrosis, focal	1 (2%)		
Hyperplasia, adenomatous	1 (2%)		
HEMATOPOIETIC SYSTEM			
#Bone marrow	(46)	(47)	(45)
Hyperplasia, NOS	1 (2%)		1 (2%)
Hyperplasia, granulocytic	2 (4%)	5 (11%)	
#Spleen	(50)	(49)	(46)
Hemosiderosis			1 (2%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)
Hematopoiesis	42 (84%)	42 (86%)	42 (91%)
#Splenic follicles	(50)	(49)	(46)
Necrosis, NOS			1 (2%)
#Lymph node	(46)	(43)	(27)
Plasmacytosis			1 (4%)
Mastocytosis	1 (2%)		
#Mandibular lymph node	(46)	(43)	(27)
Necrosis, NOS			1 (4%)
Plasmacytosis	1 (2%)	1 (2%)	
Hyperplasia, lymphoid	1 (2%)		
#Pancreatic lymph node	(46)	(43)	(27)
Hyperplasia, lymphoid	1 (2%)		
#Mesenteric lymph node	(46)	(43)	(27)
Congestion, NOS		1 (2%)	1 (4%)
Hemorrhage	5 (11%)	2 (5%)	
Hyperplasia, lymphoid	1 (2%)		
Hematopoiesis	1 (2%)	3 (7%)	

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Renal lymph node	(46)	(43)	(27)
Hyperplasia, NOS	1 (2%)		
Plasmacytosis		1 (2%)	
#Axillary lymph node	(46)	(43)	(27)
Hyperplasia, lymphoid	1 (2%)		
#Inguinal lymph node	(46)	(43)	(27)
Hyperplasia, NOS	1 (2%)		1 (4%)
Plasmacytosis			1 (4%)
#Femoral lymph node	(46)	(43)	(27)
Plasmacytosis		1 (2%)	
#Lung	(50)	(49)	(45)
Leukocytosis, NOS			1 (2%)
Leukemoid reaction	1 (2%)		
#Liver	(50)	(50)	(46)
Hematopoiesis		1 (2%)	
#Pancreas	(49)	(49)	(46)
Hematopoiesis	1 (2%)		
#Thymus	(38)	(41)	(41)
Cyst, NOS		1 (2%)	
Hemorrhage		1 (2%)	
Atrophy, NOS	1 (3%)	1 (2%)	1 (2%)
#Thymic lymphocytes	(38)	(41)	(41)
Necrosis, NOS			1 (2%)
CIRCULATORY SYSTEM			
#Inguinal lymph node	(46)	(43)	(27)
Lymphangiectasis			1 (4%)
*Lymphatics of lung	(50)	(50)	(50)
Sequestration			1 (2%)
#Lung	(50)	(49)	(45)
Thrombus, fibrin			1 (2%)
#Heart	(50)	(49)	(45)
Inflammation, suppurative			1 (2%)
Periarteritis		1 (2%)	
#Myocardium	(50)	(49)	(45)
Inflammation, chronic focal	1 (2%)		
Necrosis, focal		1 (2%)	
Calcification, NOS	1 (2%)		
#Aortic valve	(50)	(49)	(45)
Pigmentation, NOS		1 (2%)	
#Pancreas	(49)	(49)	(46)
Periarteritis	1 (2%)		
DIGESTIVE SYSTEM			
*Tooth	(50)	(50)	(50)
Congenital malformation, NOS	1 (2%)		
*Pulp of tooth	(50)	(50)	(50)
Abscess, NOS	1 (2%)		
*Alveolus dentalis	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
#Sublingual gland	(49)	(49)	(46)
Atrophy, focal	1 (2%)		
#Liver	(50)	(50)	(46)
Cyst, NOS	1 (2%)		
Hemorrhagic cyst		1 (2%)	
Inflammation, chronic focal	2 (4%)		
Necrosis, NOS	2 (4%)		
Necrosis, focal	5 (10%)	2 (4%)	1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
#Liver (Continued)	(50)	(50)	(46)
Infarct, NOS	3 (6%)	1 (2%)	
Lipoidosis	2 (4%)	2 (4%)	
Ground glass cyto change	2 (4%)	2 (4%)	
Focal cellular change	2 (4%)	1 (2%)	1 (2%)
Regeneration, NOS		1 (2%)	
#Portal tract	(50)	(50)	(46)
Atrophy, NOS			1 (2%)
#Liver/centrilobular	(50)	(50)	(46)
Necrosis, NOS	1 (2%)		
Lipoidosis	2 (4%)	1 (2%)	
Hepatocytomegaly	5 (10%)	17 (34%)	10 (22%)
#Liver/hepatocytes	(50)	(50)	(46)
Hyperplasia, focal	1 (2%)		
*Gallbladder	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
#Bile duct	(50)	(50)	(46)
Hyperplasia, NOS		1 (2%)	
#Pancreas	(49)	(49)	(46)
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic focal	1 (2%)		
#Pancreatic acinus	(49)	(49)	(46)
Atrophy, focal		2 (4%)	
Atrophy, diffuse		1 (2%)	
Hyperplasia, NOS			1 (2%)
#Esophagus/muscularis	(48)	(48)	(42)
Degeneration, NOS		1 (2%)	
#Esophageal adventitia	(48)	(48)	(42)
Hemorrhage	1 (2%)		
#Gastric mucosa	(46)	(48)	(43)
Necrosis, focal		1 (2%)	
#Glandular stomach	(46)	(48)	(43)
Dilatation, NOS	1 (2%)		
Ulcer, NOS		1 (2%)	
Calcification, focal			1 (2%)
Pigmentation, NOS	1 (2%)	1 (2%)	
#Gastric submucosa	(46)	(48)	(43)
Edema, NOS		1 (2%)	
Eosinophilic leukocytic infiltrate	1 (2%)		
#Forestomach	(46)	(48)	(43)
Ulcer, NOS		1 (2%)	
Inflammation, acute focal	1 (2%)		
Inflammation, chronic focal			1 (2%)
Necrosis, focal	1 (2%)		
Hyperplasia, epithelial		1 (2%)	
#Colonic serosa	(44)	(46)	(41)
Hemorrhage		1 (2%)	
#Cecum	(44)	(46)	(41)
Ulcer, NOS		1 (2%)	
*Anus	(50)	(50)	(50)
Ulcer, NOS			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(49)	(46)
Calculus, gross observation only		1 (2%)	
Mineralization	4 (8%)	1 (2%)	1 (2%)
Cast, NOS	1 (2%)		
Hydronephrosis	1 (2%)		1 (2%)
Pyelonephritis, NOS		3 (6%)	1 (2%)
Lymphocytic inflammatory infiltrate	2 (4%)	3 (6%)	

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney (Continued)	(50)	(49)	(46)
Plasma cell infiltrate	1 (2%)		
Metaplasia, osseous	2 (4%)	1 (2%)	
#Kidney/cortex	(50)	(49)	(46)
Cyst, NOS	1 (2%)		1 (2%)
Atrophy, focal		1 (2%)	
#Kidney/tubule	(50)	(49)	(46)
Regeneration, NOS			1 (2%)
#Kidney/pelvis	(50)	(49)	(46)
Inflammation, suppurative		1 (2%)	1 (2%)
#Urinary bladder	(46)	(45)	(38)
Distention			2 (5%)
Hemorrhage		1 (2%)	
Inflammation, suppurative		1 (2%)	
Inflammation, chronic	1 (2%)		
*Urethra	(50)	(50)	(50)
Retention of content	1 (2%)		
Inflammation, necrotizing			1 (2%)
*Prostatic urethra	(50)	(50)	(50)
Hyperplasia, epithelial		1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(43)	(45)	(45)
Cyst, NOS		1 (2%)	
Hyperplasia, focal		2 (4%)	1 (2%)
#Adrenal/capsule	(50)	(49)	(44)
Hyperplasia, NOS	38 (76%)	34 (69%)	7 (16%)
#Adrenal cortex	(50)	(49)	(44)
Pigmentation, NOS		1 (2%)	
Hypertrophy, focal	3 (6%)	1 (2%)	
Hyperplasia, focal		2 (4%)	
#Adrenal medulla	(50)	(49)	(44)
Inflammation, suppurative	1 (2%)		
Hyperplasia, focal		4 (8%)	
#Periadrenal tissue	(50)	(49)	(44)
Inflammation, granulomatous		1 (2%)	
#Thyroid	(49)	(46)	(43)
Follicular cyst, NOS	1 (2%)		
Degeneration, NOS		1 (2%)	
Atrophy, focal		1 (2%)	
Hyperplasia, follicular cell		1 (2%)	
#Pancreatic islets	(49)	(49)	(46)
Hypertrophy, NOS	1 (2%)		
Hyperplasia, NOS	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*Penis	(50)	(50)	(50)
Retention of content	1 (2%)		1 (2%)
Obstruction, NOS			1 (2%)
Inflammation, NOS	1 (2%)	2 (4%)	3 (6%)
Hyperplasia, epithelial	1 (2%)		
*Prepuce	(50)	(50)	(50)
Retention of content	1 (2%)		
Obstruction, NOS			1 (2%)
Ulcer, NOS	1 (2%)		2 (4%)
Inflammation, acute	1 (2%)		2 (4%)
Abscess, NOS			1 (2%)
Necrosis, focal	1 (2%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
*Preputial gland	(50)	(50)	(50)
Retention of content	2 (4%)		1 (2%)
Cystic ducts		1 (2%)	1 (2%)
Inflammation, NOS	2 (4%)	4 (8%)	2 (4%)
Inflammation, suppurative		1 (2%)	1 (2%)
Abscess, NOS	8 (16%)	3 (6%)	4 (8%)
Hyperplasia, NOS			1 (2%)
Hyperplasia, epithelial	1 (2%)		
#Prostate	(48)	(46)	(43)
Inflammation, suppurative		2 (4%)	3 (7%)
Abscess, NOS	1 (2%)		
Inflammation, chronic	1 (2%)	1 (2%)	
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal			1 (2%)
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS	4 (8%)	5 (10%)	
#Testis	(49)	(49)	(46)
Calcification, focal	16 (33%)	14 (29%)	10 (22%)
Atrophy, NOS	1 (2%)	1 (2%)	
Hyperplasia, interstitial cell	1 (2%)		
#Testis/tubule	(49)	(49)	(46)
Cytomegaly		1 (2%)	
*Epididymis	(50)	(50)	(50)
Granuloma, spermatic		2 (4%)	
NERVOUS SYSTEM			
#Brain	(50)	(49)	(47)
Calcification, focal	30 (60%)	21 (43%)	9 (19%)
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
*Sternum	(50)	(50)	(50)
Necrosis, NOS	2 (4%)		
*Skeletal muscle	(50)	(50)	(50)
Degeneration, NOS			1 (2%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Hemorrhage	1 (2%)	1 (2%)	
Inflammation, suppurative	2 (4%)	4 (8%)	
Abscess, NOS	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Foreign material, NOS	2 (4%)	3 (6%)	
*Peritoneum	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
*Pleura	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)	2 (4%)	
Inflammation, acute/chronic	1 (2%)	1 (2%)	
*Epicardium	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
*Mesentery	(50)	(50)	(50)
Necrosis, fat	2 (4%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
Tail			
Granuloma, NOS		1	
SPECIAL MORPHOLOGY SUMMARY			
Auto/necropsy/no histo			3

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE

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TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	2		1
ANIMALS NECROPSIED	48	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	50	49
INTEGUMENTARY SYSTEM			
*Skin	(48)	(50)	(49)
Basal cell carcinoma		1 (2%)	
*Subcutaneous tissue	(48)	(50)	(49)
Fibrosarcoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(48)	(50)	(49)
Alveolar/bronchiolar adenoma	1 (2%)	5 (10%)	1 (2%)
Alveolar/bronchiolar carcinoma	2 (4%)		
Adenosquamous carcinoma, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(48)	(50)	(49)
Malignant lymphoma, lymphocytic type	4 (8%)	3 (6%)	1 (2%)
Malignant lymphoma, histiocytic type	3 (6%)	3 (6%)	1 (2%)
Malignant lymphoma, mixed type	6 (13%)	7 (14%)	
Lymphocytic leukemia		1 (2%)	
Granulocytic leukemia	1 (2%)		
#Mesenteric lymph node	(43)	(49)	(39)
Malignant lymphoma, NOS			1 (3%)
Malignant lymphoma, mixed type	1 (2%)		
#Duodenum	(46)	(47)	(34)
Malignant lymphoma, histiocytic type		1 (2%)	
#Thymus	(46)	(44)	(49)
Sarcoma, NOS		1 (2%)	
CIRCULATORY SYSTEM			
*Multiple organs	(48)	(50)	(49)
Hemangiosarcoma	1 (2%)		
*Mediastinum	(48)	(50)	(49)
Hemangioma	1 (2%)		
#Ovary	(44)	(48)	(49)
Hemangioma		1 (2%)	
#Adrenal	(48)	(50)	(49)
Hemangioma			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(48)	(50)	(49)
Hepatocellular adenoma	3 (6%)	5 (10%)	
#Forestomach	(47)	(49)	(46)
Papilloma, NOS	1 (2%)		
URINARY SYSTEM			
None			

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(46)	(50)	(45)
Carcinoma, NOS	1 (2%)		
Adenoma, NOS	5 (11%)	3 (6%)	
#Adrenal	(48)	(50)	(49)
Cortical adenoma		1 (2%)	
#Adrenal/capsule	(48)	(50)	(49)
Adenoma, NOS	1 (2%)		
#Adrenal medulla	(48)	(50)	(49)
Pheochromocytoma		1 (2%)	
#Thyroid	(47)	(49)	(40)
Follicular cell adenoma			1 (3%)
#Pancreatic islets	(47)	(50)	(49)
Islet cell adenoma	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(48)	(50)	(49)
Adenoma, NOS	1 (2%)		
Adenocarcinoma, NOS		2 (4%)	1 (2%)
Adenosquamous carcinoma			1 (2%)
#Uterus/endometrium	(48)	(50)	(49)
Adenocarcinoma, NOS		2 (4%)	
#Ovary	(44)	(48)	(49)
Granulosa cell tumor	1 (2%)	2 (4%)	
Tubular adenoma		1 (2%)	
NERVOUS SYSTEM			
#Brain	(48)	(50)	(49)
Carcinoma, NOS, invasive	1 (2%)		
#Cerebellum	(48)	(50)	(49)
Neoplasm, NOS			1 (2%)
SPECIAL SENSE ORGANS			
*Harderian gland	(48)	(50)	(49)
Adenoma, NOS	1 (2%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Abdominal wall	(48)	(50)	(49)
Sarcoma, NOS		1 (2%)	
ALL OTHER SYSTEMS			
None			

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	4	5	17
Moribund sacrifice	3	9	7
Terminal sacrifice	41	30	2
Dosing accident		4	22
Accidentally killed, nda		2	1
Animal missing	2		1
TUMOR SUMMARY			
Total animals with primary tumors**	27	31	8
Total primary tumors	36	42	9
Total animals with benign tumors	14	14	3
Total benign tumors	15	18	3
Total animals with malignant tumors	18	20	5
Total malignant tumors	20	22	5
Total animals with secondary tumors##	1		1
Total secondary tumors	1		1
Total animals with tumors uncertain-- benign or malignant	1	2	1
Total uncertain tumors	1	2	1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE: VEHICLE CONTROL

ANIMAL NUMBER	042	043	024	028	010	008	018	017	038	001	002	003	004	005	007	008	009	011	012	013	014	015	018	019	020
WEEKS ON STUDY	043	044	061	063	092	093	099	102	121	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma										X															
RESPIRATORY SYSTEM																									
Lungs and bronchi	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X														
Alveolar/bronchiolar carcinoma			X																						
Trachea	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	M	M	+	–	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type										X															
Thymus	M	M	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Liver	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																							X		
Bile duct	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	M	M	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	M	M	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	M	M	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																									
Small intestine	M	M	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	M	M	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	M	M	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS									X																
Adenoma, NOS													X			X									
Adrenal	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																X									
Thyroid	M	M	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	M	M	–	–	–	+	–	+	+	+	+	+	+	–	+	–	–	–	–	–	–	+	+	+	+
Pancreatic islets	M	M	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma										X															
REPRODUCTIVE SYSTEM																									
Mammary gland	M	M	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																						X			
Uterus	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	M	M	–	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+
Granulosa cell tumor																									
NERVOUS SYSTEM																									
Brain	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive									X																
SPECIAL SENSE ORGANS																									
Harderian gland	M	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
BODY CAVITIES																									
Mediastinum	M	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangioma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	M	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma																									
Malignant lymphoma, lymphocytic type					X			X			X														
Malignant lymphoma, histiocytic type			X				X								X										
Malignant lymphoma, mixed type																							X	X	
Granulocytic leukemia																									

+: Tissue examined microscopically
–: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed

.: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

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TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER / WEEKS ON STUDY	0211 1035	0212 1035	0213 1035	0215 1035	0217 1035	0218 1035	0219 1035	0220 1035	0221 1035	0222 1035	0223 1035	0224 1035	0225 1035	0227 1035	0228 1035	0229 1035	0240 1035	0241 1035	0244 1035	0245 1035	0246 1035	0247 1035	0248 1035	0249 1035	0250 1035	TOTAL: TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*48
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma														X												1
Alveolar/bronchiolar carcinoma																										2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	◆	+	+	+	43
Malignant lymphoma, mixed type																										1
Thymus	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular adenoma										X							X									3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*48
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Papilloma, NOS			X																							1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma, NOS																										1
Adenoma, NOS	X												X						X							5
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid	+	+	–	+	–	+	+	–	–	+	–	–	+	–	+	–	–	+	+	–	+	+	+	+	+	37
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*48
Adenoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Granulosa cell tumor								X																		1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS, invasive																										1
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*48
Adenoma, NOS																							X			1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*48
Hemangioma								X																		1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*48
Hemangiosarcoma																				X						1
Malignant lymphoma, lymphocytic type																						X				4
Malignant lymphoma, histiocytic type																										3
Malignant lymphoma, mixed type	X	X			X					X																6
Granulocytic leukemia																									X	1

* Animals necropsied

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TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE: LOW DOSE

ANIMAL NUMBER	022	038	041	011	052	017	063	031	057	045	025	048	018	048	054	058	028	029	008	015	061	062	034	052	006
WEEKS ON STUDY	016	035	035	036	065	074	052	093	095	095	094	095	097	098	098	100	102	102	103	104	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																							X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X								X		X						
Trachea	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Thymus	+	+	+	+	–	–	–	+	+	–	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+
Sarcoma, NOS													X												
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																						X	X		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	–	+	+	+	+	+	+
Malignant lymphoma, histiocytic type																									
Large intestine	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	–	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																									
Thyroid	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	–	–	–	+	–	–	+	+	+	–	–	–	–	+	+	–	–	–	+	–	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																							X	X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+
Granulosa cell tumor																									
Tubular adenoma																							X		
Hemangioma													X												
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									X
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS													X												
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type			X														X								
Malignant lymphoma, histiocytic type										X		X			X										
Malignant lymphoma, mixed type							X													X					
Lymphocytic leukemia						X																			

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TABLE D8. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	091	092	093	094	095	096	097	098	099	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																															
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*30
Basal cell carcinoma																															1
RESPIRATORY SYSTEM																															
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X															X												5
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																															
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Sarcoma, NOS																															1
CIRCULATORY SYSTEM																															
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																															
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X								X																		X		5
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Malignant lymphoma, histiocytic type																			X												1
Large intestine	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																															
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																															
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS		X																X											X		3
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma		X																													1
Pheochromocytoma																			X												1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	32
REPRODUCTIVE SYSTEM																															
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*30
Adenocarcinoma, NOS																		X											X		2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																															2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Granulosa cell tumor																									X	X					2
Tubular adenoma																															1
Hemangioma																															1
NERVOUS SYSTEM																															
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																															
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*30
Adenoma, NOS																															1
BODY CAVITIES																															
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*30
Sarcoma, NOS																															1
ALL OTHER SYSTEMS																															
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*30
Malignant lymphoma, lymphocytic type									X																						3
Malignant lymphoma, histiocytic type								X					X		X				X												3
Malignant lymphoma, mixed type																															7
Lymphocytic leukemia																														X	1

* Animals necropsied

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TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE: HIGH DOSE

ANIMAL NUMBER	0 0 8	0 0 2	0 0 6	0 1 6	0 1 6	0 0 9	0 0 1	0 0 3	0 0 4	0 0 5	0 0 7	0 0 8	0 1 1	0 1 4	0 1 5	0 1 7	0 1 8	0 1 9	0 2 0	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5	0 3 1
WEEKS ON STUDY	0 1 6	0 1 6	0 1 8	0 3 2	0 3 4	0 4 2	0 4 4	0 4 5	0 4 5	0 4 5	0 4 5	0 4 5	0 4 5	0 4 5	0 4 5	0 4 5	0 4 5	0 4 5	0 4 5	0 4 5	0 4 5	0 4 5	0 4 5	0 4 5	0 4 5
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X												
Adenosquamous carcinoma, metastatic																									
Trachea	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	–	–	M	+	+	–	+	–	+	+	–	–	–	+	–	+	+	+	+	+	+	+	–	–	+
Malignant lymphoma, NOS																									
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	M	+	+	+	+	+	N	N	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+
Pancreas	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	–	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	M	–	–	+	+	–	+	+	+	+	–	–	–	–	+	–	+	+	+	+	–	+	+
Large intestine	+	+	M	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+
URINARY SYSTEM																									
Kidney	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Thyroid	+	+	M	+	+	+	+	+	–	+	+	+	–	+	–	+	–	–	–	+	+	+	+	–	–
Follicular cell adenoma																									
Parathyroid	–	–	M	–	–	+	+	–	–	+	–	+	–	+	–	+	–	–	–	–	–	–	+	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Adenosquamous carcinoma																									
Uterus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	M	+	(	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplasm, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type				X																					
Malignant lymphoma, histiocytic type																									

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TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	0 2 3	0 2 3	0 2 4	0 2 4	0 2 5	0 2 5	0 2 5	0 2 5	0 2 5	0 2 5	0 2 5	0 2 5	0 2 5	0 2 5	0 2 5	0 2 5	0 2 5	0 2 5	0 2 5	0 2 5	0 2 5	0 2 5	0 2 5	0 3 4	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	0 2 4	0 2 4	0 2 4	0 2 4	0 3 5	0 3 5	0 3 6	0 3 6	0 3 6	0 3 6	0 3 6	0 3 6	0 3 6	0 3 6	0 3 6	0 3 6	0 3 6	0 3 6	0 3 6	0 3 6	0 3 6	0 3 6	0 3 6	1 0 5	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																									1
Adenosquamous carcinoma, metastatic													X												1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	39
Malignant lymphoma, NOS																	X								1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	46
Small intestine	+	+	+	+	–	+	–	–	–	+	+	+	+	+	–	+	–	+	–	+	+	+	+	+	34
Large intestine	+	+	+	+	–	+	–	–	–	+	+	+	+	+	–	+	–	+	+	–	+	+	+	+	40
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	–	+	–	+	+	+	+	+	43
ENDOCRINE SYSTEM																									
Pituitary	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	45
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma													X												1
Thyroid	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Follicular cell adenoma																							X		1
Parathyroid	–	+	–	–	–	+	–	+	+	+	–	+	–	+	+	–	+	–	–	+	+	–	+	–	19
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Adenocarcinoma, NOS																					X				1
Adenosquamous carcinoma													X												1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplasm, NOS						X																			1
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Malignant lymphoma, lymphocytic type																						X			1
Malignant lymphoma, histiocytic type																									1

* Animals necropsied

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TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE

	Vehicle Control	1,000 mg/kg	2,000 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	1/48 (2%)	5/50 (10%)	1/49 (2%)
Adjusted Rates (b)	2.4%	14.0%	2.3%
Terminal Rates (c)	1/41 (2%)	2/30 (7%)	0/2 (0%)
Week of First Observation	105	93	45
Life Table Tests (d)	P=0.051	P=0.062	P=0.514
Incidental Tumor Tests (d)	P=0.292	P=0.194	P=0.984N
Cochran-Armitage Trend Test (d)	P=0.585N		
Fisher Exact Test (d)		P=0.112	P=0.747N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/48 (6%)	5/50 (10%)	1/49 (2%)
Adjusted Rates (b)	6.9%	14.0%	2.3%
Terminal Rates (c)	2/41 (5%)	2/30 (7%)	0/2 (0%)
Week of First Observation	61	93	45
Life Table Tests (d)	P=0.224	P=0.250	P=0.683
Incidental Tumor Tests (d)	P=0.403N	P=0.526	P=0.153N
Cochran-Armitage Trend Test (d)	P=0.254N		
Fisher Exact Test (d)		P=0.381	P=0.301N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	4/48 (8%)	3/50 (6%)	1/49 (2%)
Adjusted Rates (b)	9.1%	8.1%	2.1%
Terminal Rates (c)	2/41 (5%)	1/30 (3%)	0/2 (0%)
Week of First Observation	92	35	32
Life Table Tests (d)	P=0.585	P=0.610N	P=0.619
Incidental Tumor Tests (d)	P=0.020N	P=0.242N	P=0.157N
Cochran-Armitage Trend Test (d)	P=0.126N		
Fisher Exact Test (d)		P=0.477N	P=0.175N
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	3/48 (6%)	4/50 (8%)	1/49 (2%)
Adjusted Rates (b)	6.6%	10.6%	33.3%
Terminal Rates (c)	1/41 (2%)	1/30 (3%)	0/2 (0%)
Week of First Observation	61	93	103
Life Table Tests (d)	P=0.224	P=0.409	P=0.475
Incidental Tumor Tests (d)	P=0.441N	P=0.499N	P=0.616N
Cochran-Armitage Trend Test (d)	P=0.243N		
Fisher Exact Test (d)		P=0.523	P=0.301N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	7/48 (15%)	7/50 (14%)	0/49 (0%)
Adjusted Rates (b)	17.1%	21.9%	0.0%
Terminal Rates (c)	7/41 (17%)	6/30 (20%)	0/2 (0%)
Week of First Observation	105	93	
Life Table Tests (d)	P=0.520	P=0.380	P=0.632N
Incidental Tumor Tests (d)	P=0.582	P=0.443	P=0.632N
Cochran-Armitage Trend Test (d)	P=0.011N		
Fisher Exact Test (d)		P=0.581N	P=0.006N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	14/48 (29%)	14/50 (28%)	3/49 (6%)
Adjusted Rates (b)	30.9%	37.0%	42.9%
Terminal Rates (c)	10/41 (24%)	8/30 (27%)	0/2 (0%)
Week of First Observation	61	35	32
Life Table Tests (d)	P=0.150	P=0.311	P=0.213
Incidental Tumor Tests (d)	P=0.118N	P=0.397N	P=0.127N
Cochran-Armitage Trend Test (d)	P=0.004N		
Fisher Exact Test (d)		P=0.538N	P=0.003N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	1,000 mg/kg	2,000 mg/kg
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (a)	15/48 (31%)	15/50 (30%)	3/49 (6%)
Adjusted Rates (b)	33.1%	38.4%	42.9%
Terminal Rates (c)	11/41 (27%)	8/30 (27%)	0/2 (0%)
Week of First Observation	61	35	32
Life Table Tests (d)	P=0.165	P=0.305	P=0.228
Incidental Tumor Tests (d)	P=0.062N	P=0.396N	P=0.120N
Cochran-Armitage Trend Test (d)	P=0.002N		
Fisher Exact Test (d)		P=0.534N	P=0.002N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	3/48 (6%)	5/50 (10%)	0/49 (0%)
Adjusted Rates (b)	7.3%	16.7%	0.0%
Terminal Rates (c)	3/41 (7%)	5/30 (17%)	0/2 (0%)
Week of First Observation	105	105	
Life Table Tests (d)	P=0.301	P=0.199	P=0.844N
Incidental Tumor Tests (d)	P=0.301	P=0.199	P=0.844N
Cochran-Armitage Trend Test (d)	P=0.126N		
Fisher Exact Test (d)		P=0.381	P=0.118N
Pituitary Gland: Adenoma			
Overall Rates (a)	5/46 (11%)	3/50 (6%)	0/45 (0%)
Adjusted Rates (b)	12.5%	10.0%	0.0%
Terminal Rates (c)	5/40 (13%)	3/30 (10%)	0/2 (0%)
Week of First Observation	105	105	
Life Table Tests (d)	P=0.426N	P=0.521N	P=0.719N
Incidental Tumor Tests (d)	P=0.426N	P=0.521N	P=0.719N
Cochran-Armitage Trend Test (d)	P=0.022N		
Fisher Exact Test (d)		P=0.311N	P=0.029N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	6/46 (13%)	3/50 (6%)	0/45 (0%)
Adjusted Rates (b)	14.5%	10.0%	0.0%
Terminal Rates (c)	5/40 (13%)	3/30 (10%)	0/2 (0%)
Week of First Observation	102	105	
Life Table Tests (d)	P=0.312N	P=0.397N	P=0.649N
Incidental Tumor Tests (d)	P=0.239N	P=0.309N	P=0.541N
Cochran-Armitage Trend Test (d)	P=0.010N		
Fisher Exact Test (d)		P=0.203N	P=0.014N
Ovary: Granulosa Cell Tumor or Tubular Adenoma			
Overall Rates (a)	1/44 (2%)	3/48 (6%)	0/49 (0%)
Adjusted Rates (b)	2.6%	10.0%	0.0%
Terminal Rates (c)	1/39 (3%)	3/30 (10%)	0/2 (0%)
Week of First Observation	105	105	
Life Table Tests (d)	P=0.295	P=0.216	P=0.982N
Incidental Tumor Tests (d)	P=0.295	P=0.216	P=0.982N
Cochran-Armitage Trend Test (d)	P=0.344N		
Fisher Exact Test (d)		P=0.342	P=0.473N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	2		1
ANIMALS NECROPSIED	48	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	50	49
INTEGUMENTARY SYSTEM			
*Skin	(43)	(50)	(49)
Epidermal inclusion cyst		1 (2%)	
Ulcer, NOS		1 (2%)	
Inflammation, chronic focal		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(48)	(50)	(49)
Inflammation, suppurative		1 (2%)	
Inflammation, acute/chronic		1 (2%)	
*Nasal gland	(48)	(50)	(49)
Necrosis, focal	1 (2%)		
*Nasal turbinate	(48)	(50)	(49)
Reaction, foreign body			1 (2%)
#Bronchial mucous gland	(48)	(50)	(49)
Dilatation, NOS	1 (2%)		
#Lung	(48)	(50)	(49)
Atelectasis			1 (2%)
Congestion, NOS		2 (4%)	14 (29%)
Hemorrhage		1 (2%)	
Lymphocytic inflammatory infiltrate	2 (4%)	1 (2%)	3 (6%)
Inflammation, chronic focal			1 (2%)
#Lung/alveoli	(48)	(50)	(49)
Histiocytosis	2 (4%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
#Bone marrow	(48)	(49)	(49)
Granuloma, NOS			1 (2%)
Myelofibrosis	34 (71%)	37 (76%)	9 (18%)
Hyperplasia, granulocytic	1 (2%)		
#Spleen	(48)	(50)	(49)
Hemosiderosis	2 (4%)	6 (12%)	3 (6%)
Hyperplasia, lymphoid	6 (13%)	2 (4%)	3 (6%)
Hematopoiesis	37 (77%)	45 (90%)	46 (94%)
#Splenic follicles	(48)	(50)	(49)
Necrosis, NOS		2 (4%)	
#Lymph node	(43)	(49)	(39)
Hemorrhage		1 (2%)	
Hyperplasia, NOS			1 (3%)
Plasmacytosis		1 (2%)	
Hyperplasia, lymphoid	1 (2%)		
#Mandibular lymph node	(43)	(49)	(39)
Fibrosis	1 (2%)		
#Mediastinal lymph node	(43)	(49)	(39)
Hyperplasia, NOS	1 (2%)		
#Lumbar lymph node	(43)	(49)	(39)
Histiocytosis		1 (2%)	
Plasmacytosis		1 (2%)	1 (3%)
#Mesenteric lymph node	(43)	(49)	(39)
Hemorrhage	1 (2%)		
Histiocytosis			1 (3%)
Hyperplasia, lymphoid			1 (3%)
#Lung	(48)	(50)	(49)
Hematopoiesis		1 (2%)	

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Liver	(48)	(50)	(49)
Hematopoiesis			1 (2%)
#Ileum	(46)	(47)	(34)
Hyperplasia, lymphoid			1 (3%)
#Thymus	(46)	(44)	(49)
Inflammation, suppurative		1 (2%)	
Atrophy, NOS	1 (2%)		
Hyperplasia, lymphoid	1 (2%)		
CIRCULATORY SYSTEM			
#Lung	(48)	(50)	(49)
Embolism, NOS	1 (2%)		
#Myocardium	(48)	(50)	(49)
Degeneration, NOS		1 (2%)	
#Cardiac valve	(48)	(50)	(49)
Pigmentation, NOS			1 (2%)
*Aorta	(48)	(50)	(49)
Calcification, focal		1 (2%)	
#Liver	(48)	(50)	(49)
Thrombus, fibrin		1 (2%)	
#Pancreas	(47)	(50)	(49)
Periarteritis		1 (2%)	
DIGESTIVE SYSTEM			
*Intestinal tract	(48)	(50)	(49)
Infarct, NOS	1 (2%)		
#Salivary gland	(47)	(49)	(49)
Fibrosis		1 (2%)	
#Liver	(48)	(50)	(49)
Lymphocytic inflammatory infiltrate	3 (6%)		
Inflammation, chronic focal	3 (6%)		2 (4%)
Necrosis, focal	1 (2%)	2 (4%)	
Lipoidosis		2 (4%)	
Cytoplasmic vacuolization	1 (2%)		
Basophilic cyto change	1 (2%)	2 (4%)	
Ground glass cyto change	3 (6%)	3 (6%)	
Focal cellular change			1 (2%)
Angiectasis	1 (2%)		
#Liver/centrilobular	(48)	(50)	(49)
Necrosis, NOS		1 (2%)	
Hepatocytomegaly	1 (2%)		
#Liver/periportal	(48)	(50)	(49)
Necrosis, NOS	1 (2%)		
Atrophy, NOS	1 (2%)		
*Gallbladder	(48)	(50)	(49)
Inflammation, suppurative	1 (2%)		
#Pancreas	(47)	(50)	(49)
Dilatation/ducts	2 (4%)	2 (4%)	
Cyst, NOS	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Metamorphosis, fatty		2 (4%)	
#Pancreatic acinus	(47)	(50)	(49)
Necrosis, focal		1 (2%)	
Cytoplasmic vacuolization	1 (2%)		
Atrophy, NOS	2 (4%)		
Atrophy, focal		1 (2%)	
#Esophageal adventitia	(47)	(50)	(48)
Inflammation, suppurative		1 (2%)	

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Gastric fundal gland	(47)	(49)	(46)
Retention of content		1 (2%)	
#Glandular stomach	(47)	(49)	(46)
Dilatation, NOS	1 (2%)	2 (4%)	
Ulcer, NOS		1 (2%)	
Inflammation, chronic	1 (2%)		
Calcification, focal			1 (2%)
#Gastric submucosa	(47)	(49)	(46)
Cyst, NOS		1 (2%)	
#Forestomach	(47)	(49)	(46)
Ulcer, NOS		1 (2%)	
Inflammation, focal	1 (2%)		
Erosion			1 (2%)
Hyperplasia, epithelial		1 (2%)	
#Peyer's patch	(46)	(47)	(34)
Ulcer, NOS		1 (2%)	
Inflammation, acute/chronic		1 (2%)	
#Duodenum	(46)	(47)	(34)
Polyp, NOS		1 (2%)	
*Rectum	(48)	(50)	(49)
Ulcer, NOS		1 (2%)	
URINARY SYSTEM			
#Kidney	(48)	(50)	(49)
Hydronephrosis	1 (2%)		
Pyelonephritis, NOS		1 (2%)	
Lymphocytic inflammatory infiltrate	2 (4%)		2 (4%)
Metaplasia, osseous	2 (4%)	2 (4%)	
#Kidney/cortex	(48)	(50)	(49)
Atrophy, focal		3 (6%)	1 (2%)
#Renal papilla	(48)	(50)	(49)
Calcification, NOS			1 (2%)
#Urinary bladder	(46)	(49)	(43)
Lymphocytic inflammatory infiltrate	1 (2%)		1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(46)	(50)	(45)
Hyperplasia, NOS		1 (2%)	
Hyperplasia, focal	9 (20%)	8 (16%)	1 (2%)
Angiectasis		1 (2%)	
#Adrenal	(48)	(50)	(49)
Congestion, NOS			2 (4%)
Hemorrhage	1 (2%)		
Atrophy, brown	1 (2%)		
#Adrenal/capsule	(48)	(50)	(49)
Hyperplasia, NOS	44 (92%)	43 (86%)	18 (37%)
Hyperplasia, focal		1 (2%)	
#Adrenal cortex	(48)	(50)	(48)
Hemorrhage		1 (2%)	
Degeneration, NOS	1 (2%)		
Hypertrophy, focal		1 (2%)	
Hyperplasia, focal		2 (4%)	
Metaplasia, osseous	1 (2%)		
#Adrenal medulla	(48)	(50)	(49)
Hemorrhage		1 (2%)	
Hyperplasia, focal	2 (4%)	1 (2%)	

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(47)	(49)	(40)
Atrophy, focal	1 (2%)	1 (2%)	
Hyperplasia, C-cell		1 (2%)	
Hyperplasia, follicular cell	1 (2%)	1 (2%)	
#Parathyroid	(27)	(32)	(19)
Hyperplasia, focal	1 (4%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(48)	(50)	(49)
Lactation		1 (2%)	
*Mammary duct	(48)	(50)	(49)
Hyperplasia, NOS			1 (2%)
*Mammary lobule	(48)	(50)	(49)
Hyperplasia, NOS	2 (4%)		
#Uterus	(48)	(50)	(49)
Dilatation, NOS		2 (4%)	
Inflammation, suppurative		1 (2%)	1 (2%)
Abscess, NOS	1 (2%)		
Polyp, NOS			1 (2%)
#Cervix uteri	(48)	(50)	(49)
Inflammation, suppurative	1 (2%)		1 (2%)
Inflammation, chronic	1 (2%)		
Hyperplasia, epithelial	3 (6%)		1 (2%)
#Uterus/endometrium	(48)	(50)	(49)
Hyperplasia, NOS		1 (2%)	
Hyperplasia, cystic	45 (94%)	43 (86%)	35 (71%)
#Endometrial gland	(48)	(50)	(49)
Dilatation, NOS		1 (2%)	
#Uterus/myometrium	(48)	(50)	(49)
Degeneration, mucoid		1 (2%)	
#Ovary/parovarian	(44)	(48)	(49)
Fibrosis	1 (2%)		
#Ovary	(44)	(48)	(49)
Cyst, NOS	8 (18%)	11 (23%)	
Hemorrhagic cyst	1 (2%)		
Abscess, NOS	3 (7%)	1 (2%)	2 (4%)
Inflammation, acute/chronic			1 (2%)
Atrophy, NOS		1 (2%)	1 (2%)
NERVOUS SYSTEM			
#Brain/meninges	(48)	(50)	(49)
Perivascular cuffing			1 (2%)
#Brain	(48)	(50)	(49)
Epidermal inclusion cyst	1 (2%)		
Hemorrhage			1 (2%)
Calcification, focal	24 (50%)	24 (48%)	13 (27%)
SPECIAL SENSE ORGANS			
*Eye	(48)	(50)	(49)
Cataract		1 (2%)	
*Eye/cornea	(48)	(50)	(49)
Inflammation, chronic focal		1 (2%)	
*Nasolacrimal duct	(48)	(50)	(49)
Inflammation, suppurative			2 (4%)
*Ear	(48)	(50)	(49)
Inflammation, suppurative		1 (2%)	

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYL METHYLPHOSPHONATE (Continued)

	Vehicle Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
*Sternum	(48)	(50)	(49)
Necrosis, NOS	1 (2%)	1 (2%)	
BODY CAVITIES			
*Mediastinum	(48)	(50)	(49)
Inflammation, suppurative		3 (6%)	1 (2%)
Foreign material, NOS		2 (4%)	
*Abdominal cavity	(48)	(50)	(49)
Inflammation, suppurative			1 (2%)
*Peritoneum	(48)	(50)	(49)
Inflammation, suppurative	1 (2%)	1 (2%)	
*Pericardium	(48)	(50)	(49)
Inflammation, suppurative		2 (4%)	
Foreign material, NOS		1 (2%)	
ALL OTHER SYSTEMS			
Tail			
Necrosis, NOS		1	
SPECIAL MORPHOLOGY SUMMARY			
Animal missing/no necropsy	2		1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX E

GENETIC TOXICOLOGY OF DIMETHYL METHYLPHOSPHONATE

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TABLE E1. MUTAGENICITY OF DIMETHYL METHYLPHOSPHONATE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/plate (b)					
		−S9		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA100	0	129 ± 4.3	130 ± 6.2	125 ± 1.7	132 ± 4.4	142 ± 6.1	129 ± 0.9
	100	138 ± 3.8	135 ± 8.7	141 ± 9.4	118 ± 5.0	145 ± 8.3	133 ± 4.7
	333	138 ± 3.1	117 ± 7.0	137 ± 11.0	119 ± 6.8	145 ± 5.8	118 ± 10.7
	1,000	140 ± 9.3	133 ± 2.7	143 ± 11.6	132 ± 4.3	151 ± 6.9	140 ± 6.7
	3,333	142 ± 6.5	129 ± 6.6	129 ± 11.1	135 ± 7.6	136 ± 4.0	125 ± 10.1
	10,000	149 ± 9.3	138 ± 2.8	131 ± 2.6	132 ± 3.5	135 ± 3.4	127 ± 4.6
	Trial Summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	1,066 ± 24.3	934 ± 19.0	891 ± 18.7	527 ± 84.8	784 ± 10.7	650 ± 67.0
TA1535	0	26 ± 2.3	26 ± 2.4	11 ± 2.3	12 ± 1.5	13 ± 3.3	12 ± 1.9
	100	25 ± 3.8	25 ± 2.6	8 ± 0.7	8 ± 0.9	13 ± 2.1	10 ± 0.3
	333	27 ± 5.0	21 ± 2.5	8 ± 1.2	10 ± 1.7	11 ± 1.2	13 ± 0.9
	1,000	26 ± 2.6	26 ± 3.2	9 ± 1.3	9 ± 1.9	13 ± 1.2	13 ± 1.7
	3,333	28 ± 3.2	25 ± 2.3	10 ± 0.6	8 ± 1.9	11 ± 1.2	9 ± 0.6
	10,000	27 ± 4.7	22 ± 1.5	12 ± 0.7	12 ± 1.9	14 ± 2.6	10 ± 2.1
	Trial Summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	823 ± 9.9	689 ± 35.2	59 ± 6.8	30 ± 3.3	62 ± 8.5	27 ± 2.2
TA1537	0	7 ± 0.7	6 ± 1.5	4 ± 1.3	8 ± 0.9	8 ± 0.9	11 ± 2.6
	100	8 ± 1.2	5 ± 2.3	8 ± 0.6	9 ± 1.8	5 ± 0.7	9 ± 2.1
	333	7 ± 0.3	5 ± 1.3	8 ± 0.3	9 ± 2.7	7 ± 2.3	7 ± 0.6
	1,000	4 ± 0.6	5 ± 1.0	7 ± 1.2	9 ± 3.5	7 ± 0.3	8 ± 1.2
	3,333	10 ± 2.2	7 ± 0.3	7 ± 0.6	9 ± 2.7	11 ± 2.3	6 ± 0.7
	10,000	6 ± 1.5	8 ± 0.0	5 ± 1.2	9 ± 1.7	8 ± 0.7	10 ± 0.3
	Trial Summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	231 ± 57.3	294 ± 52.6	68 ± 8.2	74 ± 4.8	52 ± 4.7	63 ± 4.2
TA98	0	21 ± 0.3	19 ± 3.4	31 ± 2.6	30 ± 2.6	31 ± 3.2	28 ± 1.7
	100	20 ± 1.5	14 ± 0.9	30 ± 3.6	27 ± 0.7	38 ± 4.1	23 ± 3.8
	333	22 ± 3.1	15 ± 3.8	26 ± 3.2	27 ± 1.9	35 ± 2.9	21 ± 4.4
	1,000	21 ± 4.4	15 ± 0.3	32 ± 3.1	30 ± 3.0	31 ± 2.3	31 ± 4.3
	3,333	24 ± 4.1	17 ± 3.5	33 ± 2.3	23 ± 2.2	25 ± 2.0	27 ± 2.0
	10,000	18 ± 2.2	18 ± 5.1	25 ± 2.6	25 ± 1.0	34 ± 3.2	20 ± 1.5
	Trial Summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (c)	1,352 ± 60.1	1,129 ± 34.0	816 ± 30.5	396 ± 61.9	697 ± 6.7	447 ± 41.3

(a) Study performed at EG&G Mason Research Institute. The detailed protocol is presented in Haworth et al. (1983). Cells and study compound or solvent (distilled water) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.

TABLE E2. MUTAGENICITY OF DIMETHYL METHYLPHOSPHONATE IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (µl/ml)	Cloning Efficiency (percent)	Relative Total Growth	Mutant Count	Mutant Fraction (c)
-S9					
Trial 1					
Distilled water		67.5 ± 5.0	100.0 ± 5.4	86.0 ± 1.9	43.3 ± 3.0
Dimethyl methylphosphonate					
	(d) 0.25	62.0 ± 13.6	106.7 ± 14.1	62.3 ± 5.2	36.3 ± 6.2
	0.5	63.7 ± 2.0	87.7 ± 5.8	94.3 ± 5.6	49.3 ± 1.3
	1.0	64.7 ± 12.0	75.7 ± 12.8	108.7 ± 10.2	58.0 ± 5.9
	1.5	70.3 ± 11.3	61.0 ± 10.0	157.7 ± 22.4	75.3 ± 5.9
	3.0	74.7 ± 6.6	76.0 ± 7.4	185.0 ± 5.1	(e) 83.3 ± 4.9
	5.0	78.7 ± 5.2	69.0 ± 6.7	209.7 ± 15.4	(e) 89.7 ± 10.7
Methyl methanesulfonate					
	5.0 µg/ml	54.7 ± 10.5	36.7 ± 10.9	592.0 ± 27.2	(e) 387.0 ± 68.2
Trial 2					
Distilled water		85.8 ± 6.5	100.3 ± 10.7	58.8 ± 3.9	23.5 ± 3.1
Dimethyl methylphosphonate					
	0.25	76.3 ± 7.7	83.0 ± 7.2	87.7 ± 12.2	(e) 40.7 ± 10.2
	0.5	58.3 ± 11.6	73.7 ± 7.9	83.3 ± 12.2	(e) 48.7 ± 4.1
	1.0	59.0 ± 3.0	72.5 ± 10.5	87.5 ± 13.5	(e) 50.5 ± 10.5
	(d) 2.0	66.7 ± 4.2	67.3 ± 3.3	105.0 ± 5.0	(e) 53.0 ± 2.5
	3.0	61.0 ± 5.5	62.3 ± 6.4	116.7 ± 19.2	(e) 62.7 ± 5.8
	5.0	86.5 ± 6.5	48.5 ± 4.5	198.0 ± 12.0	(e) 77.0 ± 10.0
Methyl methanesulfonate					
	5.0 µg/ml	72.7 ± 5.9	50.3 ± 3.2	315.3 ± 22.1	(e) 145.3 ± 2.8

(a) Study performed at Litton Bionetics, Inc. The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.

(b) Mean ± standard error of replicate trials of approximately 3×10^6 cells each. All data are evaluated statistically for both trend and peak response. Both responses must be significantly ($P<0.05$) positive for a chemical to be considered mutagenic. If only one of these responses is significant, the call is "questionable"; the absence of both trend and peak response results in a "negative" call.

(c) Mutant fraction (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF per 1×10^6 cells treated); MF = mutant fraction.

(d) Acidic pH shift at this and all higher doses for this trial

(e) Significant positive response; occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1.6.

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY DIMETHYL METHYLPHOSPHONATE (a)

	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/cell (percent) (b)
−S9 (c)								
Study Performed at Environmental Health Research and Testing Laboratory								
Trial No. 1--Summary: Positive								
Medium		50	1,034	375	0.36	7.5	26.5	
Dimethyl methylphosphonate	160	50	1,032	370	0.36	7.4	26.5	98.7
	500	50	1,038	446	0.43	8.9	26.5	118.7
	1,600	50	1,039	580	0.56	11.6	26.5	154.7
	5,000	50	1,036	884	0.85	17.7	26.5	236.0
Mitomycin C	0.01	50	1,042	2,461	2.36	49.2	26.5	656.0
Trial No. 2--Summary: Positive								
Medium		50	1,033	378	0.37	7.6	26.0	
Dimethyl methylphosphonate	2,000	50	1,038	580	0.56	11.6	26.0	152.6
	3,000	50	1,031	679	0.66	13.6	26.0	178.9
	4,000	50	1,003	729	0.73	14.6	26.0	192.1
	5,000	50	1,023	845	0.83	16.9	26.0	222.4
Mitomycin C	0.005	50	1,039	1,301	1.25	26.0	26.0	342.1
+S9 (d)								
Study Performed at Environmental Health Research and Testing Laboratory								
Trial No. 1--Summary: Negative								
Medium		50	1,042	383	0.37	7.7	26.5	
Dimethyl methylphosphonate	160	50	1,049	376	0.36	7.5	26.5	97.4
	500	50	1,046	393	0.38	7.9	26.5	102.6
	1,600	50	1,052	415	0.39	8.3	26.5	107.8
	5,000	50	1,048	401	0.38	8.0	26.5	103.9
Cyclophosphamide	1.5	50	1,052	1,123	1.07	22.5	26.5	292.2
Trial No. 2--Summary: Negative								
Medium		50	1,044	437	0.42	8.7	26.0	
Dimethyl methylphosphonate	2,000	50	1,029	447	0.43	8.9	26.0	102.3
	3,000	50	1,027	409	0.40	8.2	26.0	94.3
	4,000	50	1,045	397	0.38	7.9	26.0	90.8
	5,000	50	1,028	435	0.42	8.7	26.0	100.0
Cyclophosphamide	1.5	50	1,042	1,430	1.37	28.6	26.0	328.7

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY DIMETHYL METHYLPHOSPHONATE (Continued)

	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/cell (percent) (b)
−S9 (c)								
Study performed at Litton Bionetics, Inc.								
Trial No. 1--Summary: Positive								
Water		50	1,021	383	0.38	7.7	25.5	
Dimethyl methylphosphonate	1,100	50	1,034	402	0.39	8.0	25.5	103.9
	3,667	50	1,031	679	0.66	13.6	25.5	176.6
	11,000	50	1,024	1,365	1.33	27.3	25.5	354.5
Mitomycin C	0.001	50	1,040	545	0.52	10.9	25.5	141.6
	0.010	5	104	202	1.94	40.4	25.5	524.7
+S9 (d)								
Study performed at Litton Bionetics, Inc.								
Trial No. 1--Summary: Weakly positive								
Water		50	1,035	420	0.41	8.4	25.5	
Dimethyl methylphosphonate	1,100	50	1,031	403	0.39	8.1	25.5	96.4
	3,670	50	1,036	409	0.39	8.2	25.5	97.6
	11,000	50	1,036	504	0.49	10.1	25.5	120.2
Cyclophosphamide	0.3	50	1,040	628	0.60	12.6	25.5	150.0
	2	5	103	129	1.25	25.8	25.5	307.1
Trial No. 2--Summary: Positive								
Medium		50	1,033	409	0.40	8.2	25.5	
Dimethyl methylphosphonate	14,300	50	1,019	515	0.51	10.3	25.5	125.6
	17,600	50	1,037	617	0.59	12.3	25.5	150.0
	22,000	50	1,032	624	0.60	12.5	25.5	152.4
Cyclophosphamide	0.3	50	1,031	564	0.55	11.3	25.5	137.8
	2	5	103	104	1.01	20.8	25.5	253.7

(a) SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent as described in (c) and (d) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake off, fixed, air dried, and stained.

(b) SCEs/cell in treated culture expressed as a percent of the SCEs/cell in the control culture

(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.

(d) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE E4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY DIMETHYL METHYLPHOSPHONATE (a)

Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Environmental Health Research and Testing Laboratory Study				
−S9 (b)--Harvest time: 12.0 hours				
Medium	100	0	0.00	0
Dimethyl methylphosphonate				
2,000	100	0	0.00	0
3,000	100	2	0.02	2
4,000	100	2	0.02	2
5,000	100	3	0.03	3
Summary: Negative				
Mitomycin C				
0.500	100	96	0.96	57
+S9 (c)--Harvest time: 12.0 hours				
Medium	100	0	0.00	0
Dimethyl methylphosphonate				
2,000	100	0	0.00	0
3,000	100	4	0.04	3
4,000	100	3	0.03	3
5,000	100	2	0.02	2
Summary: Negative				
Cyclophosphamide				
50	100	57	0.57	39
Litton Bionetics, Inc., Study				
−S9--Harvest time: 10.5 hours				
Medium	100	2	0.02	2
Dimethyl methylphosphonate				
16,500	100	1	0.01	1
19,300	100	5	0.05	4
22,000	100	5	0.05	5
Summary: Negative				
Mitomycin C				
0.500	50	9	0.18	16
+S9--Harvest time: 10.5 hours				
Medium	100	0	0.00	0
Dimethyl methylphosphonate				
14,300	100	1	0.01	1
17,600	100	0	0.00	0
22,000	100	3	0.03	3
Summary: Negative				
Cyclophosphamide				
25	50	23	0.46	26

(a) Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or medium as indicated in (b) and (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake off, fixed, and stained in 6% Giemsa.

(b) In the absence of S9, cells were incubated with study compound or medium for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.

(c) In the presence of S9, cells were incubated with study compound or medium for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation prior to harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE E5. INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN DROSOPHILA BY DIMETHYL METHYLPHOSPHONATE (a)

Route of Exposure	Dose (ppm)	Incidence of Deaths (percent)	Incidence of Sterility (percent)	No. of Lethals/No. of X Chromosomes Tested			Overall Total (b)
				Mating 1	Mating 2	Mating 3	
Feeding	23,735	57	0	19/2,012	21/3,250	2/716	42/5,978 (0.70%)
	0			1/2,003	3/2,929	1/942	5/5,874 (0.09%)

(a) Study performed at Brown University. A detailed protocol of the sex-linked recessive lethal assay is presented in Zimmering et al. (1985). Exposure by feeding was done by allowing 24-hour-old Canton-S males to feed for 3 days on a solution of the study chemical dissolved in 5% sucrose. Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three broods of 3, 2, and 2 days; sample sperm from successive matings were treated as spermatozoa (mating 1), spermatids (mating 2), and spermatocytes (mating 3). F_1 heterozygous females were crossed to their siblings and placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters; no clusters were found. After 17 days, presumptive lethal mutations were identified as vials containing no wild-type males; these were retested. Results were significant at the 5% level (Margolin et al., 1983).
(b) Combined total of number of lethal mutations/number of X chromosomes tested for three mating trials

TABLE E6. INDUCTION OF RECIPROCAL TRANSLOCATIONS IN DROSOPHILA BY DIMETHYL METHYLPHOSPHONATE (a)

Route of Exposure	Dose (ppm)	Transfers (translocations/total F_1 tested)					Total No. of Tests	Total No. of Translocations	Total Translocations (percent)
		1	2	3	4	5			
Feeding	23,500	0/2,466	0/2,323	0/2,953	0/900	0/131	8,773	0	0.0000
Historical control	0						104,844	2	0.0019

(a) Study performed at Brown University. A detailed protocol of the reciprocal translocation assay is presented in Zimmering et al. (1985). Exposed males were mated to three bw;st females for 3 days and discarded. The females were transferred to fresh medium every 3-4 days to produce a total of five cultures, and then they were discarded. In this manner, sample sperm from successive cultures were stored for increasing lengths of time. Individual F_1 males were backcrossed to bw;st females, and the F_2 generation was screened for pseudolinkage. This procedure allows the recovery of translocations involving the Y, second, or third chromosomes in any combination. Presumptive translocations were retested. Results were not significant at the 5% level (Kastenbaum and Bowman, 1970).

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APPENDIX F

SENTINEL ANIMAL PROGRAM

APPENDIX F. SENTINEL ANIMAL PROGRAM

I. Methods

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via viral serology on sera from extra (sentinel) animals in the study rooms. These animals are untreated, and these animals and the study animals are both subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Fifteen B6C3F$_1$ mice and 15 F344/N rats of each sex are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected vehicle control animals of each sex and species. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the antibody titers. The following tests are performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai	M.Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) MHV (mouse hepatitis virus)	MHV *M. Pul. (Mycoplasma pulmonis)*
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai (6, 18, 24 mo)	RCV (rat coronavirus) Sendai (12 mo)	

II. Results

Five of 10 mice tested at 18 months had a positive serologic reaction for *Mycoplasma pulmonis*. No positive results were seen at 6, 12, 18, or 24 months in rats or at 6, 12, or 24 months in mice.

Mycoplasma pulmonis infection-related lesions were not observed in the rats and mice in these studies. Further evaluation of the reagents used for detection of *M. pulmonis* by ELISA indicated that the reagents may not be specific for detection of antibodies to *M. pulmonis*.

APPENDIX G

INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Pellet Diet: April 1981 to September 1983

(Manufactured by Zeigler Bros., Inc., Gardners, PA)

		PAGE
TABLE G1	INGREDIENTS OF NIH 07 RAT AND MOUSE RATION	166
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TABLE G3	NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION	167
TABLE G4	CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION	168

TABLE G1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

Ingredients (b)	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Brewer's dried yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

(a) NIH, 1978; NCI, 1976
(b) Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed

TABLE G2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione activity
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 µg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

(a) Per ton (2,000 lb) of finished product

TABLE G3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	23.63 ± 0.85	22.2-25.3	29
Crude fat (percent by weight)	4.9 ± 0.51	3.3-5.7	29
Crude fiber (percent by weight)	3.33 ± 0.25	2.9-3.8	29
Ash (percent by weight)	6.51 ± 0.43	5.7-7.31	29
Essential Amino Acids (percent of total diet)			
Arginine	1.323 ± 0.830	1.21-1.39	4
Cystine	0.310 ± 0.099	0.218-0.400	4
Glycine	1.155 ± 0.069	1.06-1.21	4
Histidine	0.572 ± 0.030	0.530-0.603	4
Isoleucine	0.910 ± 0.033	0.881-0.944	4
Leucine	1.949 ± 0.065	1.85-1.99	4
Lysine	1.275 ± 0.076	1.20-1.37	4
Methionine	0.422 ± 0.187	0.306-0.699	4
Phenylalanine	0.909 ± 0.167	0.665-1.04	4
Threonine	0.844 ± 0.029	0.824-0.886	4
Tryptophan	0.187	0.171-0.211	3
Tyrosine	0.631 ± 0.094	0.566-0.769	4
Valine	1.11 ± 0.050	1.05-1.17	4
Essential Fatty Acids (percent of total diet)			
Linoleic	2.44	2.37-2.52	3
Linolenic	0.274	0.256-0.308	3
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	11,655 ± 4,113	7,500-24,000	29
Vitamin D (IU/kg)	4,650	3,000-6,300	2
α-Tocopherol (ppm)	41.53 ± 7.52	31.1-48.9	4
Thiamine (ppm)	16.2 ± 2.17	12.0-21.0	28
Riboflavin (ppm)	7.5 ± 0.96	6.1-8.2	4
Niacin (ppm)	85.0 ± 14.2	65.0-97.0	4
Pantothenic acid (ppm)	29.3 ± 4.6	23.0-34.0	4
Pyridoxine (ppm)	7.6 ± 1.5	5.6-8.8	4
Folic acid (ppm)	2.8 ± 0.88	1.8-3.7	4
Biotin (ppm)	0.27 ± 0.05	0.21-0.32	4
Vitamin B_{12} (ppb)	21.0 ± 11.9	11.0-38.0	4
Choline (ppm)	3,302.0 ± 120.0	3,200.0-3,430.0	4
Minerals			
Calcium (percent)	1.25 ± 0.12	1.08-1.53	29
Phosphorus (percent)	0.99 ± 0.05	0.88-1.11	29
Potassium (percent)	0.862 ± 0.100	0.772-0.974	3
Chloride (percent)	0.546 ± 0.100	0.442-0.635	4
Sodium (percent)	0.311 ± 0.038	0.258-0.350	4
Magnesium (percent)	0.169 ± 0.133	0.151-0.181	4
Sulfur (percent)	0.316 ± 0.070	0.270-0.420	4
Iron (ppm)	447.0 ± 57.3	409.0-523.0	4
Manganese (ppm)	90.6 ± 8.20	81.7-95.5	4
Zinc (ppm)	53.6 ± 5.27	46.1-58.6	4
Copper (ppm)	10.77 ± 3.19	8.09-15.39	4
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.81 ± 0.28	1.44-2.09	4
Cobalt (ppm)	0.68 ± 0.14	0.49-0.80	4

TABLE G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (a)

Contaminant	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.50 ± 0.13	0.29-0.77	29
Cadmium (ppm) (a)	<0.10	<0.1-0.1	29
Lead (ppm) (b)	0.71 ± 0.39	0.33-1.97	27
Lead (ppm) (c)	0.87 ± 0.71	0.33-3.37	29
Mercury (ppm) (a)	<0.05		29
Selenium (ppm)	0.29 ± 0.06	0.13-0.40	29
Aflatoxins (ppb) (d)	<10	<5.0-<10.0	29
Nitrate nitrogen (ppm) (e)	9.55 ± 4.46	<0.1-22.0	29
Nitrite nitrogen (ppm) (f)	2.25 ± 1.77	<0.1-7.2	29
BHA (ppm) (g)	5.43 ± 4.72	0.4-17.0	29
BHT (ppm) (h)	2.7 ± 1.82	<1.0-12.0	28
	3.0 ± 2.5	<1.0-5.9	29
Aerobic plate count (CFU/g)	46,810 ± 34,504	6,600-130,000	29
Coliform (MPN/g) (i)	13.25 ± 21.07	<3-93	28
Coliform (MPN/g) (j)	28.66 ± 85.50	<3-460	29
E. coli (MPN/g)	<3	<2-3	29
Total nitrosamines (ppb) (k,l)	3.44 ± 2.68	0.8-9.3	28
Total nitrosamines (ppb) (k,m)	12.96 ± 51.33	0.8-279.5	29
N-Nitrosodimethylamine (ppb) (k,n)	2.78 ± 2.39	0.8-8.3	28
N-Nitrosodimethylamine (ppb) (k,o)	12.27 ± 51.16	0.8-278.0	29
N-Nitrosopyrrolidine (ppb) (p)	1.16 ± 0.49	<0.9-2.9	25
Pesticides (ppm)			
α-BHC (a,q)	<0.01		29
β-BHC (a)	<0.02		29
γ-BHC-Lindane (a)	<0.01		29
δ-BHC (a)	<0.01		29
Heptachlor (a)	<0.01		29
Aldrin (a)	<0.01		29
Heptachlor epoxide (a)	<0.01		29
DDE (a)	<0.01		29
DDD (a)	<0.01		29
DDT (a)	<0.01		29
HCB (a)	<0.01		29
Mirex (a)	<0.01		29
Methoxychlor (r)	<0.05	0.09 (8/26/81); 0.06 (7/26/83)	29
Dieldrin (a)	<0.01		29
Endrin (a)	<0.01		29
Telodrin (a)	<0.01		29
Chlordane (a)	<0.05		29
Toxaphene (a)	<0.1		29
Estimated PCBs (a)	<0.2		29
Ronnel (a)	<0.01		29
Ethion (a)	<0.02		29
Trithion (a)	<0.05		29
Diazinon (a)	<0.1		29
Methyl parathion (a)	<0.02		29
Ethyl parathion (a)	<0.02		29
Malathion (a)	0.10 ± 0.09	<0.05-0.42	29
Endosulfan I (a)	<0.01		29
Endosulfan II (a)	<0.01		29
Endosulfan sulfate (a)	<0.03		29

TABLE G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit. The detection limit is given as the mean.
(b) Excludes two high values of 2.65 ppm and 3.37 ppm obtained in batches produced on 8/26/81 and on 7/21/82.
(c) Includes the high values given in b.
(d) The detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(e) Sources of contamination: alfalfa, grains, and fish meal
(f) Sources of contamination: soy oil and fish meal
(g) Mean, standard deviation, and range exclude one very high value of 12.0 obtained for the batch produced on 11/23/82.
(h) Mean, standard deviation, and range include the high value listed in footnote g.
(i) MPN = most probable number; mean, standard deviation, and range exclude one very high value of 460 MPN/g obtained in the batch produced on 9/23/82.
(j) Mean, standard deviation, and range include the high value listed in footnote i.
(k) All values were corrected for percent recovery.
(l) Mean, standard deviation, and range exclude one very high value of 279.5 ppb obtained for the batch produced on 4/27/81.
(m) Mean, standard deviation, and range include the high value listed in footnote l.
(n) Mean, standard deviation, and range exclude one very high value of 278 obtained for the batch produced on 4/27/81.
(o) Mean, standard deviation, and range include the high value given in footnote n.
(p) Samples analyzed from batches produced on 6/22/83, 7/26/83, 8/17/83, and 9/20/83 were below the detection limit (1.0 ppb).
(q) BHC = hexachlorocyclohexane or benzene hexachloride
(r) Two observations were above the detection limit. The values and the date are given under the range.
(s) Fourteen batches contained more than 0.05 ppm.

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APPENDIX H

DATA AUDIT SUMMARY

APPENDIX H. DATA AUDIT SUMMARY

The experimental data, documents, pathology materials, and draft NTP Technical Report for the 2-year toxicology and carcinogenesis studies of dimethyl methylphosphonate in rats and mice were audited for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations of the Food and Drug Administration (implemented by the NTP beginning October 1, 1981). The laboratory experiments were conducted for the NTP by Litton Bionetics, Inc., Rockville, Maryland, under a subcontract with Tracor Jitco, Inc. Animal dosing with dimethyl methylphosphonate began in July 1981 and ended November 1983. The retrospective audit was conducted at the NTP Archives in February 1986 by Program Resources, Inc. The following individuals were involved with the audit: W.L. Oller, Ph.D. (Principal Investigator); K.A. Connor; J.E. Kovach, B.A.; S.A. Corson, H.T. (ASCP); K.M. Pace, B.S.; and C.D. Rafferty, A.S.; and the following personnel from Veritas Laboratories: J.W. Sagartz, D.V.M., ACVP; and N.J. MacLachlan, D.V.M., ACVP.

The full report of the audit is on file at the NIEHS. The audit included a review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) All chemistry records.
(3) Body weights and clinical observation data for a random 10% sample of the study animals.
(4) All inlife records concerning environmental conditions, palpable masses, mortality, and animal identification.
(5) All postmortem records for individual animals concerning identification, disposition codes, condition codes, correct data entry, and correlation between gross observations and microscopic diagnoses.
(6) Wet tissues from a random 10% sample of the study animals and from animals that had a gross observation without a corresponding microscopic diagnosis to verify animal identification and to examine for untrimmed lesions.
(7) Slides and blocks of tissues from all vehicle control and high dose animals to examine for proper match and inventory.
(8) Tabulated pathology diagnoses for a random 10% of study animals to verify computer data entry.

The audit showed that the data in the Technical Report (including inlife observations and chemistry data) reflect the data at the NTP Archives.

Animal identification was confirmed. The audit revealed untrimmed lesions in the wet tissues. All wet tissues were then examined by an NTP pathology support contractor, and any lesions found were sectioned. NTP pathology staff provided the diagnoses for these additional lesions, and these are incorporated in the Technical Report. This additional pathology evaluation and review did not change the interpretation of the studies.

The NIEHS/NTP concludes that the documents and materials at the NTP Archives support the data and results presented in this Technical Report.

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NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS
PUBLISHED AS OF OCTOBER 1987

TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	Dibromochloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane (Inhalation)
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butylbenzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-ethylhexyl)phthalate
219	2,6-Dichloro-*p*-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	D-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos
250	Benzyl Acetate
251	Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
267	Propylene Oxide
269	Telone II®
271	HC Blue No. 1
272	Propylene
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
281	H.C. Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl)phosphonium Sulfate and Tetrakis(hydroxymethyl)phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
324	Boric Acid
325	Pentachloronitrobenzene
327	Xylenes (Mixed)

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